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These are the records for the RN's I searched — labeled acc. to claims alphabetical designations. I was unable to locate compds (c) & (k)

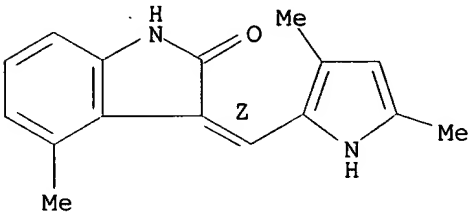
=> d 1-6

(b)

L42 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **210303-58-5** REGISTRY
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-4-methyl-, (3Z)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H16 N2 O
SR CA
LC STN Files: CA, CAPLUS

09/186,475

Double bond geometry as shown.

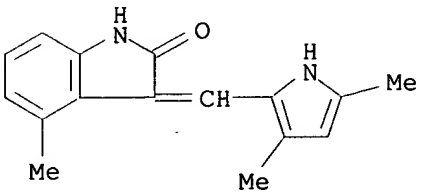


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(b)

L42 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **204005-54-9** REGISTRY
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-4-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C16 H16 N2 O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



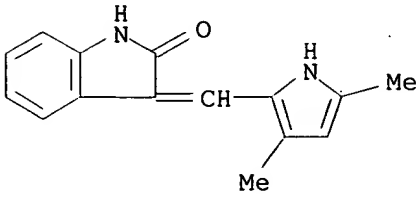
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1937 TO DATE)
2 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(a)

L42 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **204005-46-9** REGISTRY
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)
OTHER NAMES:

CN NSC 696819
CN Semoxind
CN SU 5416
CN Sugen 5416
FS 3D CONCORD
MF C15 H14 N2 O
SR CA
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CHEMCATS, DRUGPAT, DRUGUPDATES, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL



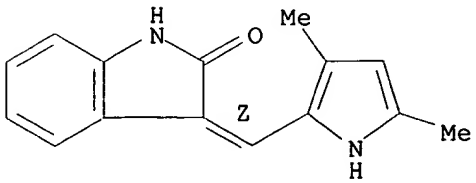
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

89 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
91 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(a)

L42 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **194413-58-6** REGISTRY
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-, (3Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-, (Z)-
OTHER NAMES:
CN 3-[1-(3,5-Dimethyl-1H-pyrrol-2-yl)meth-(Z)-ylidene]-2-oxo-2,3-dihydroindole
CN Semaxanib
FS STEREOSEARCH
MF C15 H14 N2 O
SR CAS Registry Services
LC STN Files: BIOSIS, CA, CAPLUS, CHEMLIST, DRUGPAT, DRUGUPDATES, MSDS-OHS, TOXCENTER, USAN, USPATFULL

Double bond geometry as shown.



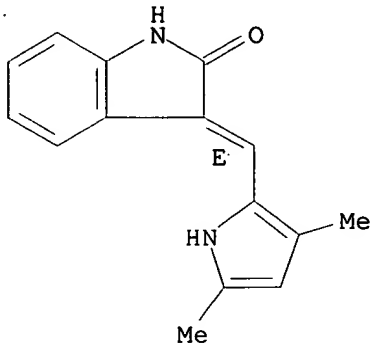
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1937 TO DATE)
8 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(c)

L42 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **194413-57-5** REGISTRY
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-, (3E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-, (E)-
FS STEREOSEARCH
MF C15 H14 N2 O
SR CAS Registry Services
LC STN Files: CA, CAPLUS

Double bond geometry as shown.

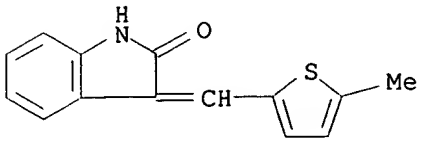


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(d)

L42 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **186610-97-9** REGISTRY
CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SU 5424
FS 3D CONCORD
MF C14 H11 N O S
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, TOXCENTER, USPAT2, USPATFULL



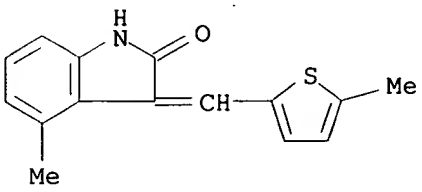
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8 REFERENCES IN FILE CAPLUS (1937 TO DATE)

=> d l43 1-6

(h)

L43 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **346405-31-0** REGISTRY
CN 2H-Indol-2-one, 1,3-dihydro-4-methyl-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C15 H13 N O S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

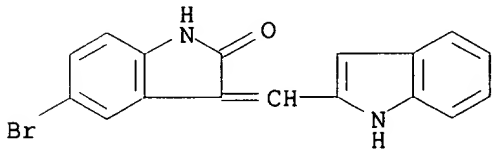


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(j)

L43 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **258830-72-7** REGISTRY
CN 2H-Indol-2-one, 5-bromo-1,3-dihydro-3-(1H-indol-2-ylmethylene)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C17 H11 Br N2 O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



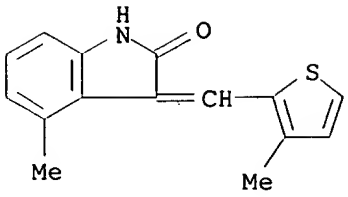
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(i)

L43 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **245036-26-4** REGISTRY
CN 2H-Indol-2-one, 1,3-dihydro-4-methyl-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4-Methyl-3-[(3-methylthiophen-2-yl)methylene]-1,3-dihydro-2H-indol-2-one
FS 3D CONCORD
MF C15 H13 N O S

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

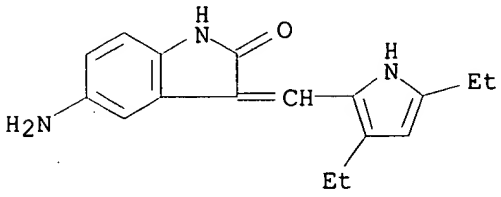


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1937 TO DATE)
2 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(g)

L43 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **204005-56-1** REGISTRY
CN 2H-Indol-2-one, 5-amino-3-[(3,5-diethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Amino-3-[(3,5-diethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydroindol-2-one
FS 3D CONCORD
MF C17 H19 N3 O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

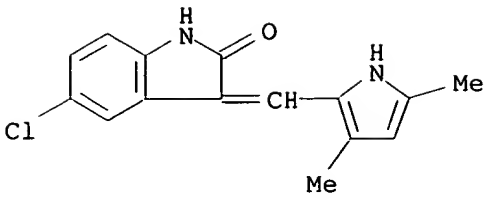


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1937 TO DATE)
2 REFERENCES IN FILE CAPLUS (1937 TO DATE)

(f)

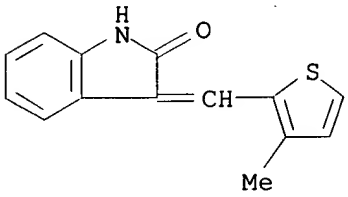
L43 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **186611-56-3** REGISTRY
CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydroindol-2-one
CN SU 5614
FS 3D CONCORD
MF C15 H13 Cl N2 O
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CSCHEM, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13 REFERENCES IN FILE CAPLUS (1937 TO DATE)

L43 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN **186610-98-0** REGISTRY
CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SU 5427
FS 3D CONCORD
MF C14 H11 N O S
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8 REFERENCES IN FILE CAPLUS (1937 TO DATE)

40 cits for Markush str.

=> d ibib abs hitstr l3 1-40

L3 ANSWER 1 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:591307 HCAPLUS
DOCUMENT NUMBER: **139:143997**
TITLE: Methods using Edg receptor modulators for the treatment of Edg receptor-associated conditions
INVENTOR(S): Shankar, Geetha; Solow-Cordero, David; Spencer, Juliet V.; Gluchowski, Charles
PATENT ASSIGNEE(S): Ceretek LLC, USA
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062392	A2	20030731	WO 2003-US1881	20030121

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-350445P P 20020118
US 2002-350446P P 20020118
US 2002-350447P P 20020118
US 2002-350448P P 20020118
OTHER SOURCE(S): MARPAT 139:143997
AB The invention provides a method of modulating an Edg-2, Edg-3, Ed-4 or Edg7 receptor-mediated biol. activity in a cell. A cell expressing the Edg-2, Edg-3, Edg-4 or Edg 7 receptor is contacted with a modulator of the Edg-2, Edg-3, Ed-4 or Edg 7 receptor sufficient to modulate receptor mediated biol. activity. In another aspect, the present invention provides a method for modulating an Edg-2, Edg-3, Ed-4 or Edg-7 receptor mediated biol. in a subject. A therapeutically effective amt. of a modulator of the Edg-2, Edg-3, Ed-4 or Edg7 receptor is administered to the subject. Prepn. of compds., e.g. 4,4,4-trifluoro-3-oxo-N-(5-phenyl-2H-pyrazol-3-yl)butyramide, is described.

L3 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:492716 HCAPLUS
DOCUMENT NUMBER: **139:63316**
TITLE: Methods using a combination of a 3-heteroaryl-2-indolinone and a cyclooxygenase-2 inhibitor for the treatment of neoplasia
INVENTOR(S): Masferrer, Jaime L.; Cherrington, Julie M.; Leahy, Kathleen M.; Zweifel, Ben S.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 66 pp., Cont.-in-part of Appl. No. PCT/US99/30693.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003119895	A1	20030626	US 2002-150546	20020516
WO 2000038730	A2	20000706	WO 1999-US30693	19991222
WO 2000038730	A3	20001102		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-113786P P 19981223
WO 1999-US30693 A2 19991222
OTHER SOURCE(S): MARPAT 139:63316

AB The invention provides methods and compns. useful for treatment or prevention of neoplasia by administering a combination comprising a 3-heteroaryl-2-indolinone compd. (prepn. included) and a COX-2 selective inhibitor. Further provided are compns., pharmaceutical compns., and kits for treatment and prevention of neoplasia.

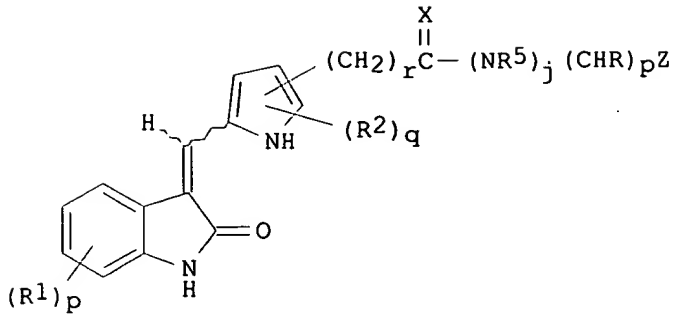
L3 ANSWER 3 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:334853 HCAPLUS
DOCUMENT NUMBER: **138:331677**
TITLE: Treatment of acute myeloid leukemia with indolinone compounds, and preparation thereof
INVENTOR(S): O'Farrell, Ann-Marie; Cherrington, Julie
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035009	A2	20030501	WO 2002-US34525	20021028

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003130280	A1	20030710	US 2002-281266	20021028

PRIORITY APPLN. INFO.: US 2001-330623P P 20011026
OTHER SOURCE(S): MARPAT 138:331677
GI



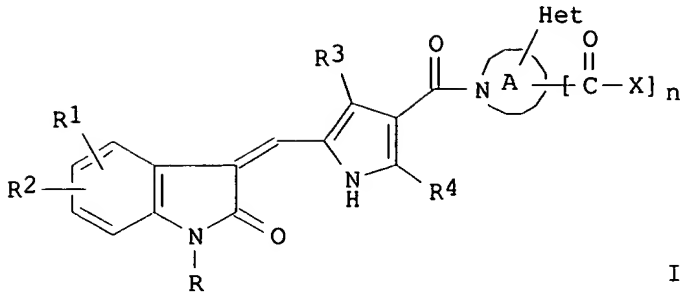
I

AB A method of treating acute myeloid leukemia in patient pos. for FLT-3-ITD is described. The treatment is accomplished by administration of an indolinone compd. (Markush included). Prepn. of the compds. of the invention, e.g. I, is described.

L3 ANSWER 4 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:301079 HCAPLUS
DOCUMENT NUMBER: **138:304310**
TITLE: Preparation of 3-[4-(heterocyclyl)-pyrrol-2-ylmethylidene]-2-indolinone derivatives as kinase inhibitors
INVENTOR(S): Mattson, Matthew; Vojkovsky, Tomas; Liang, Congxin; Tang, Peng Cho; Guan, Huiping
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031438	A1	20030417	WO 2002-US32354	20021010
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003130235	A1	20030710	US 2002-268082	20021010

PRIORITY APPLN. INFO.: US 2001-328226P P 20011010
OTHER SOURCE(S): MARPAT 138:304310
GI



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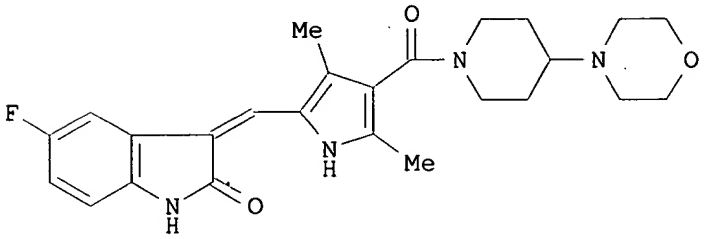


II

AB Title compds. I [R = H, PO2R5, acyl, alkyl, etc.; R1 = H, alkyl, alkoxy, OH, CF3, etc.; R2 = H, alkyl, heteroaryl, alkoxy, etc.; R3-5 = H, alkyl; A = (un)substituted heterocycloamino; Het = cycloalkylaminoalkyl, heteroaryl, etc.; X = amino, alkoxy; n = 0-1] are prepd. For instance, 4-amino-1-benzylpiperidine is converted to 4-(morpholin-4-yl)piperidine (i. DMF, K2CO3, 50.degree.; ii. MeOHaq, H2-Pd/C) and coupled to prior art (Z)-3-(3,5-dimethyl-4-carboxy-1H-pyrrol-2-ylmethylidene)-5-fluoro-1,3-dihydro-2H-indol-2-one (DMF, BOP, Et3N) to give II. I inhibit kinases, in particular **VEGFR**, PDGFR and c-KIT kinases (no data) and are useful for the treatment of glioblastoma, melanoma, etc.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:261842 HCAPLUS

DOCUMENT NUMBER: **138:287526**

TITLE: Preparation of 3-(heteroarylamino)methylene-1,3-dihydro-2H-indol-2-ones as tyrosine kinase inhibitors for regulating, modulating and/or inhibiting abnormal cell proliferation

INVENTOR(S): Andrews, Steven W.; Wurster, Julie A.; Hull, C. Eugene, III

PATENT ASSIGNEE(S): Allergan, Inc., USA

SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

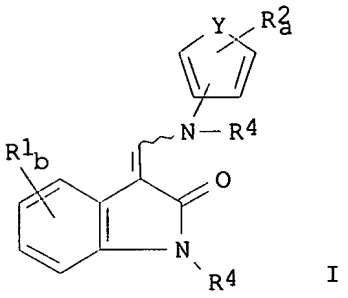
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003027109	A1	20030403	WO 2002-US29630	20020918

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-325814P P 20010927
OTHER SOURCE(S): MARPAT 138:287526
GI



I

AB The present invention relates to 3-(heteroarylamino)methylene-1,3-dihydro-2H-indol-2-ones (shown as I; variables defined below; e.g. 5-[(2-oxo-1,2-dihydroindol-3-ylidenemethyl)amino]furan-2-carboxylic acid Me ester and 4-methyl-2-[(2-oxo-1,2-dihydroindol-3-ylidenemethyl)amino]thiophene-3-carboxylic acid Et ester), capable of modulating tyrosine kinase signal transduction to regulate, modulate and/or inhibit abnormal cell proliferation. Inhibitory biol. data are presented for 2 examples of I for the following assays: **VEGF** stimulated calcium ion signal in vitro and KDR. Although the methods of prepn. are not claimed, 2 example prepns. are included. For I: R1 = halogen and C1-C4 alkyl; Y = O and S; R2 = C1-C4 alkyl and COOR3, wherein R3 = H and C1-C4 alkyl; and b = 0-2; a = 0-2; R4 = H and C1-C4 alkyl; and the wavy line = a cis or trans bond,.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:154170 HCAPLUS
DOCUMENT NUMBER: **138:180703**
TITLE: Combination therapy for the treatment of cancer
INVENTOR(S): Doshi, Parul; Cherrington, Julie
PATENT ASSIGNEE(S): Masferrer, Jaime, USA
SOURCE: PCT Int. Appl., 217 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

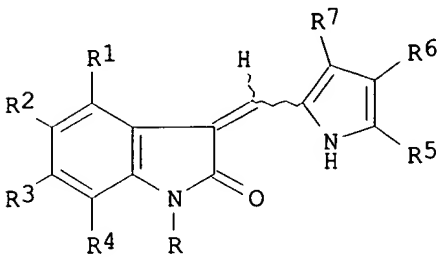
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015608	A2	20030227	WO 2002-US25797	20020815

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-312413P P 20010815
OTHER SOURCE(S): MARPAT 138:180703
GI



I

AB The present invention relates to methods for treatment or prevention of neoplasia disorders using protein tyrosine kinase inhibitors in combination with cyclooxygenase inhibitors, in particular cyclooxygenase-2 selective inhibitors. The protein kinase inhibitors are of the formula I where R = H, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, piperidin-1-ylmethyl, etc.; R1 = H, halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, etc.; R2 = hydrogen, halo, alkyl, substituted alkyl, trihalomethyl, hydroxy, alkoxy, etc.; R3 = H, halogen, alkyl, substituted alkyl, trihalomethyl, hydroxy, alkoxy, aryl, heteroaryl, etc.; R4 = H, halogen, alkyl, substituted alkyl, hydroxy, alkoxy, etc.; R5 = H, alkyl, substituted alkyl, etc.; R6 = hydrogen, alkyl, substituted alkyl, etc.; and R7 = H, alkyl, substituted alkyl, aryl, heteroaryl, etc.

L3 ANSWER 7 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:5770 HCAPLUS
DOCUMENT NUMBER: **138:56076**
TITLE: Preparation of phosphorus-substituted idolinones as therapeutic agents
INVENTOR(S): Shakespeare, William C.; Sawyer, Tomi K.; Metcalf, Chester A., III; Wang, Yihan; Bohacek, Regine
PATENT ASSIGNEE(S): Ariad Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000251	A1	20030103	WO 2002-US19769	20020621
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003130234	A1	20030710	US 2002-177472	20020621

PRIORITY APPLN. INFO.: US 2001-299923P P 20010621
OTHER SOURCE(S): MARPAT 138:56076
GI

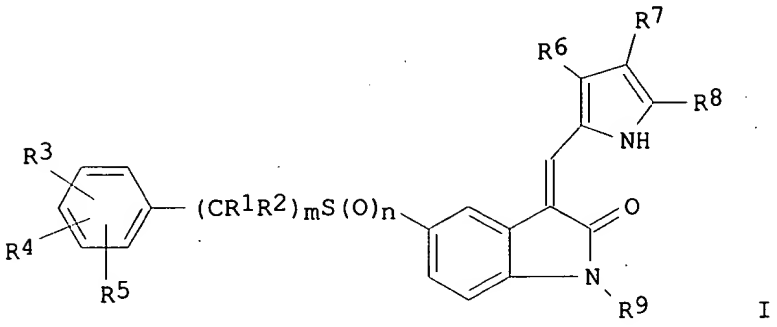
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Phosphorus-substituted idolinones [e.g, I; wherein X = O, S, amino; R1, R5 = H, aliph., heteroaliph., halo, aryl, heteroaryl, etc.; R2 = aliph., heteroaliph., aryl, heteroaryl; each R3, R4, independently = H, aliph., heteroaliph., aryl, heteroaryl, halo, cyano, NO2, alkylcarbonyl, etc.; p = 0, 1, 2, 3, 4 and q = 0, 1, 2, 3, 4, with the limitation that q + p = 0-4; at least one of R2, R3, R4 or R5 is a phosphorus-contg. moiety] were prepd. Compd. (II) is exemplary. The prepd. compds. are useful as, inter alia, anticancer agents, antiproliferative agents, and agents for the treatment of osteoporosis (no data).
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:927188 HCAPLUS
DOCUMENT NUMBER: **138:14005**
TITLE: Preparation of 5-aralkylsulfonyl-3-(pyrrol-2-ylmethylidene)-2-indolinone derivatives as kinase inhibitors
INVENTOR(S): Cui, Jingrong; Ramphal, Yudhi; Liang, Congxin; Sun, Li; Wei, Chung Chen; Tang, Peng Cho
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 479 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096361	A2	20021205	WO 2002-US16841	20020530
WO 2002096361	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003125370 A1 20030703 US 2002-157007 20020530
US 6599902 B2 20030729
PRIORITY APPLN. INFO.: US 2001-294544P P 20010530
US 2001-328408P P 20011010
OTHER SOURCE(S): MARPAT 138:14005
GI



I

AB The present invention relates to certain 5-aralkylsulfonyl-3-(pyrrol-2-ylmethylidene)-2-indolinone derivs. (shown as I; see below for variable definitions; e.g. 2,4-dimethyl-5-(2-oxo-5-phenylmethanesulfonyl-1,2-dihydroindol-(3Z)-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide) that inhibit kinases (no data), in particular met kinase. Pharmaceutical compns. comprising these compds., methods of treating diseases mediated by kinases using pharmaceutical compns. comprising these compds., and methods of prepg. them are also disclosed. In I: n = 0-2; m = 1-3; R1 and R2 = H or alkyl; R3, R4, and R5 = H, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxy, cyano, carboxy, carboxyalkyl, nitro, aryl, aryloxy, heteroaryl, heteroaryloxy, -(alkylene)-CONR10R11, -CONR10R11, or - NR10R11 (R10 is H or alkyl, and R11 is aryl, heteroaryl, heterocycle, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, aralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy, or R10 and R11 together with the N atom to which they are attached combine to form satd. or unsatd. heterocycloamino). R6 is H, alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, heterocyclylalkyl, aryl, heteroaryl, carboxy, alkoxycarbonyl, heterocyclylcarbonyl, aminoalkylcarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, -CONR10R11 or -(alkylene)-CONR10R11. R7 and R8 = H, alkyl, cycloalkyl, heterocyclylalkyl, -COR12, -(alkylene)-COR12 (R12 = alkoxy, hydroxy, or heterocycle, alkylamino, dialkylamino), -SO2R14, -CONR13R14, or -(alkylene)-CONR13R14 (R13 is H or alkyl, and R14 is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl,

cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, heteroaralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy group(s), or when R13 and R14 are attached to a N atom R13 and R14 together with the N atom to which they are attached form satd. or unsatd. heterocycloamino). R6 and R7 or R7 and R8 can combine to form a satd. or unsatd. 5 to 8 membered ring; and R9 is: H or alkyl; -PO(OR15)2 where each R15 = H or alkyl; -COR16 where R16 is H or alkyl; or -CHR17NR18R19 where R17 is H or alkyl, and R18 and R19 = H or alkyl or R18 and R19 together with the N atom to which they are attached form heterocycloamino. Although the methods of prepn. are not claimed, 375 example prepns. of I plus addnl. prepns. of intermediates are included.

L3 ANSWER 9 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:927175 HCAPLUS
DOCUMENT NUMBER: **138:14131**
TITLE: Preparation of pharmaceutical compositions containing mikanolide, dihydromikanolide or an analog thereof combined with another anticancer agent for therapeutic use in cancer treatment
INVENTOR(S): Prevost, Gregoire; Coulomb, Helene; Lavergne, Olivier; Lanco, Christophe; Teng, Beng-Poon
PATENT ASSIGNEE(S): Societe De Conseils De Recherches Et D'applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096348	A2	20021205	WO 2002-FR1800	20020529
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2825278	A1	20021206	FR 2001-7104	20010530

PRIORITY APPLN. INFO.: FR 2001-7104 A 20010530
OTHER SOURCE(S): MARPAT 138:14131
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

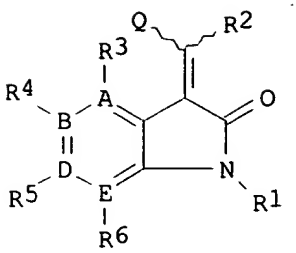
AB The invention concerns a product comprising at least mikanolide (I), dihydromikanolide or an analog, e.g., II [R1 = H, SR4, NR4R5; R2 = SR6, NR6R7; R3 = OH, O-acyl, O-silyl, O-carbamyl; R4, R6 = alkyl, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, (un)substituted aryl, aralkyl; R5, R7 = H, alkyl, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, (un)substituted aryl, aralkyl; R4R5 = 5- to 7-membered N-contg. ring] and III, or their

pharmaceutically acceptable salts, combined with at least one other anticancer agent for simultaneous, sep. or prolonged therapeutic use in cancer treatment. In a preferred embodiment of the invention, the mikanolide, dihydromikanolide or one analog thereof is combined with enzymic inhibitors such as G heterotrimeric protein inhibitors, IV [X = R22; Y = R18; XY = 6-membered ring, CHR18CHR19; R11 = H, lower alkyl, alkylthio; R12, R13 = H, lower alkyl; R14 = O, H2; R5 = H, lower alkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; R16, R17 = H, CONHCHR13CO2R14, lower alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; R18, R19 = H, lower alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; R18R19 = aryl or heterocycly ring; R20, R21 = H, aryl, heterocyclyl, alkyl, arylalkyl, heterocyclylalkyl; R22 = NR9, S, O; R23 = ; R24 = H, lower alkyl], V (R18, R19 = H, lower alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; R18R19 = aryl or heterocycly ring) or VI (R22 = NR9, S, O), or alkylating agents such as cis-platin. Thus, VII was prepd. from mikanolide. VII was tested for cell proliferation inhibition activity [only 34% of cells lived when combined with VIII.cntdot.HCl (vs. human colon cancer HT-29 cells)].

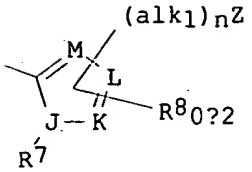
L3 ANSWER 10 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:902261 HCAPLUS
DOCUMENT NUMBER: **138:4517**
TITLE: Preparation of 3-heteroarylmethylidene-2-indolinone protein kinase inhibitors for use against cancer and other disorders
INVENTOR(S): McMahon, Gerald; Tang, Peng Cho; Sun, Li
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 64 pp., Cont.-in-part of U.S. Ser. No. 74,621.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6486185	B1	20021126	US 1998-191458	19981112
US 6316429	B1	20011113	US 1998-74621	19980507
US 2002156083	A1	20021024	US 2001-819698	20010329

PRIORITY APPLN. INFO.: US 1997-45838P P 19970507
US 1997-59677P P 19970919
US 1998-74621 A2 19980507
OTHER SOURCE(S): MARPAT 138:4517
GI



I



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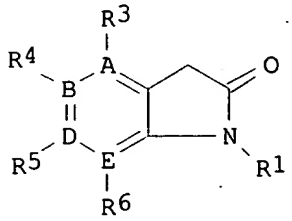
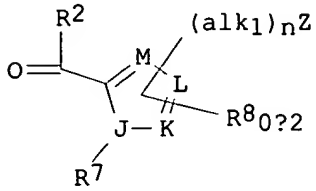


III



IV

AB The present invention relates to novel 3-heteroarylidene-2-indolinone compds. (shown as I; e.g. 3-[3-(2-carboxyethyl)-4-methylpyrrol-2-methylidene]-2-indolinone) and physiol. acceptable salts thereof which modulate the activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer. In I: A, B, D and E = C and N, it being understood that the N-contg. 9-member bicyclic ring formed is one known in the chem. arts; it being further understood that when A, B, D, or E is N, R3, R4, R5 or R6, resp., does not exist. R1 = H, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, carboxy, C-amido and sulfonyl; R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, and heteroalicyclic; R3, R4, R5 and R6 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, -SH, -S-alkyl, -S-cycloalkyl, -S-aryl, -S-heteroaryl, sulfinyl, sulfonyl, sulfonamido, carbonyl, carboxy, cyano, nitro, halo, -OC(O)NR10R11, N-carbamyl, -OC(S)NR10R11, N-thiocarbamyl, C-amido, N-amido, amino and -NR10R11; R10 and R11 = H, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring contg. at least one N; R3 and R4, R4 and R5, or R4 and R5 may combine to form a six-member aryl or heteroaryl ring. Q is a heteroaryl group II in which J = O, N and S; K, L and M = C, N, O and S such that the five-member heteroaryl ring formed is one known in the chem. arts, it being understood that when K, L and M are N, S or O, R8 or -(alk1)nZ cannot be covalently bonded to that atom; when J is N, R7 = H, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, carboxy, C-amido, guanyl and sulfonyl and when J is O or S, R7 does not exist and there is no bond; R8 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, -SH, -S-alkyl, -S-cycloalkyl, -S-aryl, -S-heteroaryl, sulfinyl, sulfonyl, sulfonamido, carbonyl, carboxy, cyano, nitro, halo, -OC(O)NR10R11, N-carbamyl, -OC(S)NR10R11, N-thiocarbamyl, C-amido, N-amido, amino, -NR10R11, trihalomethyl, a five member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring fused to two adjacent atoms of the Q ring; and a six-member cycloalkyl, aryl, heteroaryl, or heteroalicyclic ring fused to two adjacent atoms of the Q ring. R10and R11 = H, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring contg. at least one N; alk1 = optionally substituted methylene (-CRR'-), optionally substituted ethylene (-C(R):C(R')-) and acetylene (-C.tplbond.C-); R and R' = H, alkyl, cycloalkyl, aryl, alkoxy,

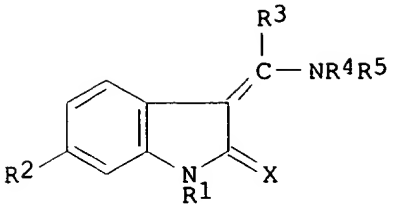
-S-alkyl, -S-cycloalkyl, aryloxy and halo. N is 0 to 10, inclusive with the proviso that when n is 0, R7 is not alkyl substituted with aryl; and Z is a polar group hydroxy, alkoxy, carboxy, nitro, cyano, carbamyl, amino, quaternary ammonium, amido, ureido, sulfonamido, sulfinyl, sulfonyl, phosphono, phosphonyl, morpholino, piperazinyl and tetrazolo. Also claimed are a combinatorial library of .gtoreq.13 I and a method for synthesizing I comprising the step of reacting III with a 2nd reactant IV in a solvent and in the presence of a base at elevated temps. The IC50 results for 12 I for PDGFR, FLK-1R, EGFR, HER2 and IGF-1R protein tyrosine kinases (PTKs) are presented; IC50 refers to that amt. of the tested compd. needed to effect a 50% inhibition of PTK activity in the test indicated with respect to a control in which no compd. of this invention is present. Thus, 3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-2-indolinone inhibited FLK-IR kinase with IC50 = 0.07 .mu.M.

REFERENCE COUNT: 211 THERE ARE 211 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:772126 HCAPLUS
DOCUMENT NUMBER: **137:279089**
TITLE: Preparation of indolinone-6-carboxylic acids as inhibitors of **endothelial** cell proliferation
INVENTOR(S): Roth, Gerald Juergen; Heckel, Armin; Lehmann-Lintz, Thorsten; Kley, Joerg; Hilberg, Frank; Van Meel, Jacobus
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: Ger. Offen., 26 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10117204	A1	20021010	DE 2001-10117204	20010406
WO 2002081445	A1	20021017	WO 2002-EP3583	20020330
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003092756	A1	20030515	US 2002-116365	20020404

PRIORITY APPLN. INFO.: DE 2001-10117204 A 20010406
OTHER SOURCE(S): MARPAT 137:279089
GI



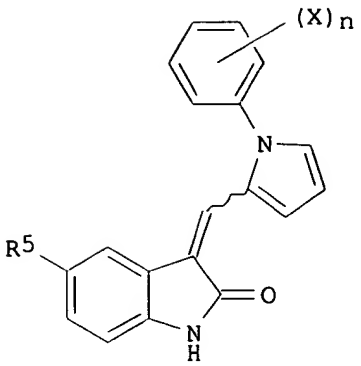
I

AB Title compds. [I; X = O, S; R1 = H, prodrug residue; R2 = CO2H, C1-6 alkoxycarbonyl, C4-7 cycloalkoxycarbonyl, aryloxycarbonyl; R3 = H, alkyl, cycloalkyl, CF3, heteroaryl, (substituted) Ph, naphthyl; R4 = (substituted) Ph, furanyl; R5 = H, alkyl], were prepd. Thus, a mixt. of 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone (prepn. given) and 4-amino-N-(2-dimethylaminoethyl)-N-methylbenzamide (analog prepn. given) in DMF was stirred for 4 h at 70.degree. followed by addn. of concd. NH3 and stirring for 30 min at room temp. to give 24% 3-(Z)-[1-(4-[(2-dimethylaminoethyl)-N-methylcarbamoyl]phenylamino)-1-phenylmethylidene]-2-indolinone-6-carboxylic acid Me ester. The latter inhibited proliferation of human umbilical cord **endothelial** cells (HUVEC) with IC50 = 0.04 .mu.M. The title compds. were said to inhibit tyrosine kinases and cyclin/CDK complexes as well as the proliferation of different tumor cells.

L3 ANSWER 12 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:716271 HCAPLUS
DOCUMENT NUMBER: **137:232554**
TITLE: Compounds derived from oxindoles with activity as inhibitors of tubulin polymerization, and the use thereof in cancerology
INVENTOR(S): Combeau, Cecile; Mailliet, Patrick; Chiron, Marielle
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072575	A1	20020919	WO 2002-FR852	20020311
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2822155	A1	20020920	FR 2001-3408	20010313

PRIORITY APPLN. INFO.: FR 2001-3408 A 20010313
OTHER SOURCE(S): CASREACT 137:232554; MARPAT 137:232554
GI



I

AB The invention relates to compds. I [wherein: R5 = -NHCOR2 or -CONHR2; R2 = C1-3 alkyl; X = Cl, Br; n = 1-3; exocyclic double bond is E, Z, or a mixt.]. I have antimitotic, antiproliferative, and antivascular properties by inhibition of the polymn. of tubulin into microtubules. Three specific compds. were prepd. in examples and claimed. For instance, condensation of 5-(acetylamino)indolin-2-one with N-(3,5-dichlorophenyl)pyrrole-2-carboxaldehyde in the presence of piperidine in refluxing EtOH gave I [R5 = NHCOMe; (X)n = 3,5-dichloro] (II) in 40% yield. This compd. inhibited the polymn. of porcine cerebral tubulin in vitro with an IC50 of 2.4 .mu.M. II also inhibited proliferation of HeLa cells in vitro with an IC50 of 0.05 .mu.M, and induced detachment of HDMEC cells in vitro by 29% at 1 .mu.M.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:658111 HCAPLUS
DOCUMENT NUMBER: **137:185408**
TITLE: 3-(4-Amidopyrrol-2-ylmethylidene)-2-indolinone derivatives as protein kinase inhibitors
INVENTOR(S): Guan, Huiping; Liang, Congxin; Sun, Li; Tang, Peng Cho; Wei, Chung Chen; Mauragis, Michael A.; Vojkovsky, Tomas; Jin, Qingwu; Herrinton, Paul Matthew
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 167 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

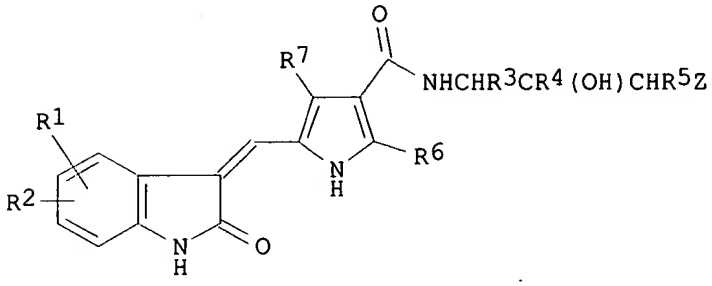
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066463	A1	20020829	WO 2002-US4407	20020215

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ŻW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003092917 A1 20030515 US 2002-76140 20020215
WO 2003070725 A2 20030828 WO 2003-US4520 20030214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-268683P P 20010215
US 2001-312361P P 20010815
WO 2002-US4407 A 20020215
US 2002-411732P P 20020918
OTHER SOURCE(S): MARPAT 137:185408

GI



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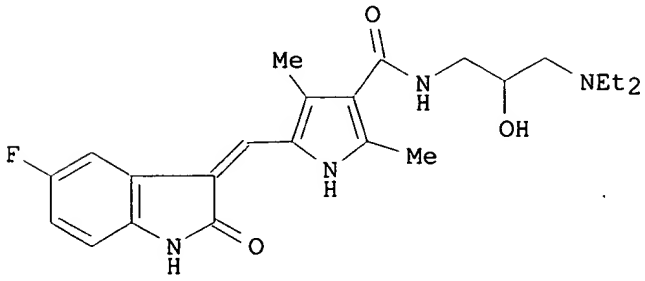


II

AB Title compds. I [R1 = H, halo, alkyl, haloalkoxy, cycloalkyl, heterocyclic, OH, alkoxy, (un)esterified CO2H, (un)substituted NH2, CONH2; R2 = H, halo, alkyl, trihalomethyl, OH, alkoxy, CN, (un)substituted NH2, SO2NH2, (un)esterified CO2H, SO2R8, R8 = alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl; R3-R6 = H, alkyl; R7 = H, alkyl, aryl, heteroaryl, acyl; Z = aryl, heteroaryl, heterocyclic, (un)substituted NH2] were prepd. for use as protein kinase inhibitors in treatment of diseases, such as cancer (no data). Thus, Et 3,5-dimethyl-4-pyrrolecarboxylate was oxidized to the 5-carboxaldehyde, followed by ester hydrolysis, reaction with

5-fluoro-2-oxindole and amidation to give the amide II.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:539677 HCAPLUS
DOCUMENT NUMBER: **137:109202**
TITLE: Preparation of 4-aryl substituted indolinones as protein kinase signal transduction modulators for inhibiting abnormal cell proliferation
INVENTOR(S): Cui, Jingrong; Zhang, Ruofei; Shen, Hong; Chu, Ji Yu; Zhang, Fang-Jie; Koenig, Marcel; Do, Steven Huy; Li, Xiaoyuan; Wei, Chung Chen; Tang, Peng Cho
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 560 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055517	A2	20020718	WO 2001-US48564	20011220
WO 2002055517	A3	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003069297	A1	20030410	US 2001-23488	20011220

PRIORITY APPLN. INFO.: US 2000-256479P P 20001220
OTHER SOURCE(S): MARPAT 137:109202
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = (un)substituted aryl or heteroaryl; R2 = H, halo, alkyl, alkenyl, alkynyl, heterocyclyl, etc.; R3 = (un)substituted pyrrole or cycloalkenylpyrrole], as well as pharmaceutical compns. thereof, are prepd. and disclosed as compds. capable of modulating protein kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Thus II, was prepd. via condensation of 4-phenyl-1,3-dihydroindol-2-one with 5-formyl-2-methyl-4-[3-(4-methylpiperazin-1-yl)propyl]-1H-pyrrole-3-carboxylic acid Et ester. I were evaluated against eight specfic kinases, e.g., FGFR1, for which I possessed IC50 values (.mu.M) of 0.0091-2.07. The present invention also relates to methods for treating protein kinase related disorders.

L3 ANSWER 15 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:89818 HCAPLUS
DOCUMENT NUMBER: **136:139851**

TITLE: Self-emulsifying drug delivery systems for extremely water-insoluble, lipophilic drugs
INVENTOR(S): Gao, Ping; Morozowich, Walter; Shenoy, Narmada
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA; Sugen, Inc.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007712	A2	20020131	WO 2001-US23140	20010720
WO 2002007712	A3	20020613		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002119198	A1	20020829	US 2001-909691	20010720
EP 1303261	A2	20030423	EP 2001-954879	20010720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-220376P P 20000724
WO 2001-US23140 W 20010720
OTHER SOURCE(S): MARPAT 136:139851

AB A self-emulsifying drug delivery system for extremely water-insol., lipophilic compds. is disclosed. Self-emulsifying drug delivery systems contg. PVP achieved 10-15% oral bioavailability of 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone compared to tablet and oil suspension formulations showing only 0-1% bioavailability.

L3 ANSWER 16 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:31440 HCAPLUS
DOCUMENT NUMBER: **136:102386**
TITLE: Preparation and use of 4-heteroaryl-3-heteroarylidenyl-2-indolinones and their use as protein kinase inhibitors
INVENTOR(S): Tang, Peng Cho; Wei, Chung Chen; Huang, Ping; Cui, Jingron
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002551	A1	20020110	WO 2001-US20768	20010629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,				

RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

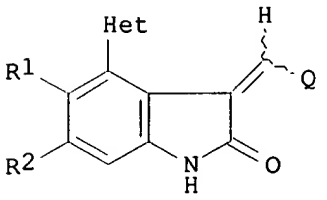
US 2002187978	A1	20021212	US 2001-894902 20010629
EP 1296975	A1	20030402	EP 2001-948830 20010629

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 2000-215654P P 20000630
WO 2001-US20768 W 20010629

OTHER SOURCE(S): MARPAT 136:102386

GI



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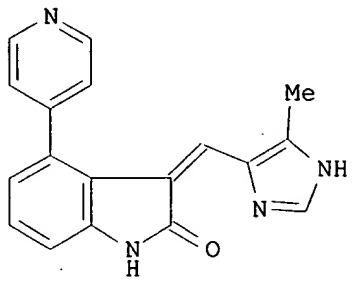

II

AB Title compds. I [R1-2 = H, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, halo, etc.; Het = (un)substituted arom. heterocycle contg. at least one and not more than two N atoms, tetrahydro(thio)pyranyl, (thio)morpholino, piperidinyl, piperazinyl, tetrazolyl, etc.; Q = (un)substituted arom. heterocycle contg. not more than two N atoms, 5-membered ring (un)substituted heterocycle contg. N, O or S, e.g., imidazolyl, pyrrolyl, indolyl, etc.] with some exceptions, were prepd. Included are 75 synthetic examples and results for several protein tyrosine kinase assays for those compds. For instance, 4-bromoindole was coupled to bis(pinacolato)diborane (DMSO, KOAc, PdCl2(dppf).bul.CH2Cl2, 80.degree.C, 22 h). The resulting dioxaborolane was coupled to 4-bromopyridine.bul.HCl (THF, Pd(PPh3)4, NaOH, 70.degree.C, 6 h) to give the indole which was treated with C5H5N.bul.Br3 (t-BuOH/EtOH/H2O, 1h) followed by zinc (stirred 1 addnl. hour) to give 4-(pyridin-4-yl)-1,3-dyhydroindol-2-one as a yellow solid. Condensation of this intermediate with 5-methylimidazole-4-carboxaldehyde (EtOH, piperidine, 2 days) afforded II. II had IC50 = 4.88 mM for FGFR-1 tyrosine kinase and 0.03 mM for cdk2/cyclin A tyrosine kinase. I are useful in treating cancer, immunol. disorders, etc.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:904107 HCAPLUS
DOCUMENT NUMBER: **136:37505**
TITLE: Preparation of 3-(2-indolylmethylene)-2-indolinones as protein kinase/phosphatase inhibitors for treatment of proliferative diseases
INVENTOR(S): Tang, Peng Cho; Harris, G. Davis; Li, Xiaoyuan
PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: PCT Int. Appl., 199 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094312	A2	20011213	WO 2001-US17961	20010604
WO 2001094312	A3	20020808		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002052369	A1	20020502	US 2001-871700	20010604
EP 1294688	A2	20030326	EP 2001-946059	20010604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-209162P P 20000602
WO 2001-US17961 W 20010604

OTHER SOURCE(S): MARPAT 136:37505

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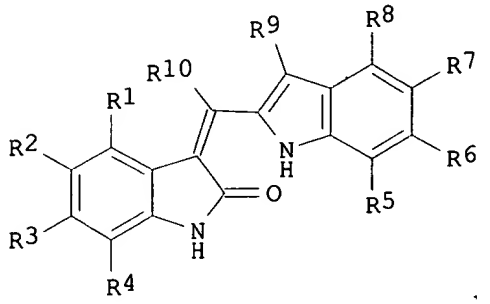

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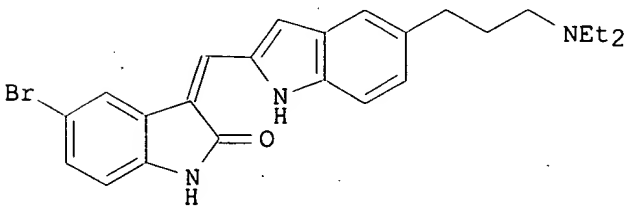

II

AB Title compds. I [wherein R4-R6 and R8-R10 = H; R1, R2, and R3 = independently H, halo, carboxylic acid, trihalomethyl, or (un)substituted ester, amide, alkyl, alkoxy, or (hetero)aryl; R7 = (un)substituted alkyl or alkoxy; or pharmaceutically acceptable salt thereof] were prepd. as modulators of the activity of protein kinases (PKs) and phosphatases. For example, 5-bromo-2-oxindole was coupled with 5-(3-diethylaminopropyl)-1H-indole-2-carbaldehyde (prepn. given) in the presence of piperidine in EtOH

to afford II, which inhibited GST-FLK-1, EGF receptor kinase, and PDGF with IC50 values of 0.03 .mu.M, 2.87 .mu.M, and 0.38 .mu.M, resp. I are useful in treating disorders related to abnormal PK activity, such as blood vessel proliferative disorders, mesangial cell proliferative disorders, fibrotic disorders, cancer, diabetes, autoimmune disorders, hyperproliferation disorders, restenosis, fibrosis, psoriasis, von Heppel-Lindau disease, osteoarthritis, rheumatoid arthritis, **angiogenesis**, inflammatory disorders, immunol. disorders, and cardiovascular disorders (no data). Combinatorial libraries comprising at least five indolinone compds., formed by reacting oxindoles with aldehydes, are also claimed.

L3 ANSWER 18 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:868450 HCAPLUS
DOCUMENT NUMBER: **136:5903**
TITLE: Preparation of 1-(pyrrolidin-1-ylmethyl)-3-(pyrrol-2-ylmethylidene)-2-indolinones as protein kinase activity modulators.
INVENTOR(S): Moon, Malcolm Wilson; Morozowich, Walter; Gao, Ping
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001090104	A2	20011129	WO 2001-US16756	20010524
WO 2001090104	A3	20020613		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002032204	A1	20020314	US 2001-863804	20010524
US 2002035140	A1	20020321	US 2001-863905	20010524
US 6451838	B2	20020917		
US 2002037878	A1	20020328	US 2001-863819	20010524
US 6482848	B2	20021119		
EP 1294711	A2	20030326	EP 2001-937687	20010524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003045565	A1	20030306	US 2002-243663	20020916
US 2003083363	A1	20030501	US 2002-243942	20020916

PRIORITY APPLN. INFO.:
US 2000-207000P P 20000524
US 2000-225045P P 20000811
US 2001-863819 A3 20010524
US 2001-863905 A1 20010524
WO 2001-US16756 W 20010524

OTHER SOURCE(S): MARPAT 136:5903
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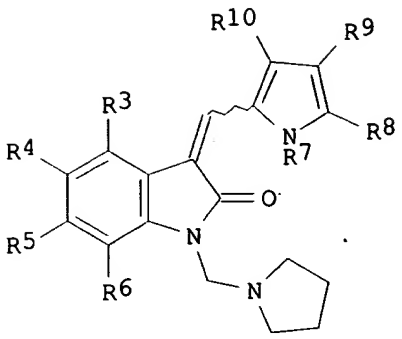

I

AB Title compds. [I; R3-R6 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, SH, alkylthio, arylthio, etc.; .gtoreq.2 of R3-R6 = H; R7 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, aryloxy, etc.; R8-R10 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, aryloxy, SH, alkylthio, arylthio, etc.], were prepd. Thus, pyrrolidine was added to a mixt. of aq. H2CO and 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylidene)-1,3-dihydroindol-2-one in MeOH; after 15 min. the mixt. was cooled to 0.degree. and filtered to give (3Z)-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1-(1-pyrrolidinylmethyl)-1,3-dihydro-2H-indol-2-one. The latter prodrug had a half life of 7.3 min. in dogs.

L3 ANSWER 19 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:868449 HCAPLUS
DOCUMENT NUMBER: **136:5902**
TITLE: Preparation of prodrugs of 3-(pyrrol-2-ylmethylidene)-2-indolinones as modulators of protein kinase activity.
INVENTOR(S): Moon, Malcolm Wilson; Morozowich, Walter; Gao, Ping; Koenig, Marcel
PATENT ASSIGNEE(S): Sugen, Inc., USA; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001090103	A2	20011129	WO 2001-US16741	20010524
WO 2001090103	A3	20020718		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002032204	A1	20020314	US 2001-863804	20010524
US 2002035140	A1	20020321	US 2001-863905	20010524
US 6451838	B2	20020917		

US 2002037878	A1	20020328	US 2001-863819	20010524	
US 6482848	B2	20021119			
EP 1283835	A2	20030219	EP 2001-939349	20010524	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2003045565	A1	20030306	US 2002-243663	20020916	
US 2003083363	A1	20030501	US 2002-243942	20020916	

PRIORITY APPLN. INFO.:
US 2000-207000P P 20000524
US 2000-225045P P 20000811
US 2001-863819 A3 20010524
US 2001-863905 A1 20010524
WO 2001-US16741 W 20010524

OTHER SOURCE(S): MARPAT 136:5902

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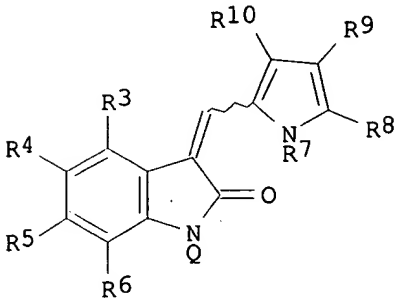

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AB Title compds. [I; R3-R6 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, aryloxy, SH, alkylthio, arylthio, etc.; .gtoreq.2 of R3-R6 = H; R3R4, R4R5, R5R6 = atoms to form aryl ring, OCH2O, OCH2OCH2; R7 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, aryloxy, etc.; R8-R10 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, aryloxy, SH, arylthio, etc.; Q = CHR11OR21, COR51, OP(O)(ORa)(ORb); R11 = H, alkyl; R21 = H, alkyl, aralkyl, acyl; R51 = alkyl; Ra, Rb = H, alkyl], were prepd. as prodrugs for modulators of protein kinase activity (no data). Thus, 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylidene)-1,3-dihydroindol-2-one was stirred 1 h with aq. H2CO and Et3N in DMF to give (3Z)-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1-hydroxymethyl-1,3-dihydro-2H-indol-2-one.

L3 ANSWER 20 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:830898 HCAPLUS
DOCUMENT NUMBER: **135:357926**
TITLE: Synthesis of indolinone vinyl-derivatives used to modulate protein kinase activity
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald; Harris, G. David
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 212,494. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6316635	B1	20011113	US 1999-293518	19990415
US 5880141	A	19990309	US 1995-485323	19950607
US 5792783	A	19980811	US 1996-655223	19960605
US 5883113	A	19990316	US 1996-659191	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
US 6225335	B1	20010501	US 1998-212494	19981215
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2001027207	A1	20011004	US 2001-765619	20010122
US 6469032	B2	20021022		
US 2002028840	A1	20020307	US 2001-899550	20010706
US 6569868	B2	20030527		
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
US 1995-485323	A2	19950607
US 1996-655223	A2	19960605
US 1996-659191	A1	19960605
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1997-915366	A3	19970820
US 1999-293518	A1	19990415
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 135:357926

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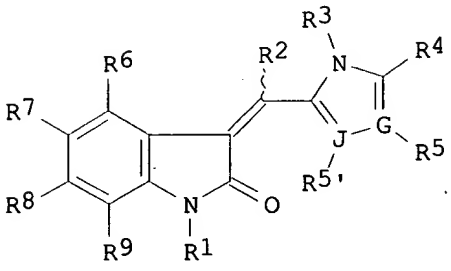

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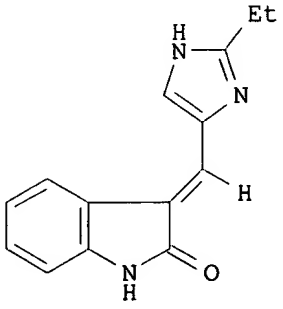

II

AB Title compds. I [G, J = N such that, when G = N, J = C and when J = N, G = C, it being recognized that, when G or J = N, R5 or R5' does not exist;

R1-3 = H; R4, R5, R5' H, alk(en/yn)yl, cycloalkyl, aryl, heteroaryl, heteroalicylic, halo, hydroxy, nitro, cyano, alkoxy, aryloxy, etc.; R6-9 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, etc.] with some exceptions, were prepd. For instance, 2-ethyl-4-formylimidazole was reacted with resin bound 2-chlorotriphenylmethyl chloride (CH2Cl2, iPr2NEt, 21 h, room temp.) and the isolated product condensed with 2-indolinone (DMF, piperidine, 80.degree.C, 20 h) to give the corresponding resin-bound 2-indolinone. The resin bound intermediate was cleaved (CH2Cl2, TFA, 2 h, room temp.) to give II as the TFA salt of a 10:1 E/Z mixt. I exhibit kinase inhibitory activity and are useful for treating, e.g., diabetes, autoimmune disorder, etc.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:617993 HCAPLUS
DOCUMENT NUMBER: **135:195497**
TITLE: Preparation of pyrrole substituted 2-indolinone protein kinase inhibitors for treatment of cancer
INVENTOR(S): Tang, Peng Cho; Miller, Todd; Li, Xiaoyuan; Sun, Li; Wei, Chung Chen; Shirazian, Shahrzad; Liang, Congxin; Vojkovsky, Tomas; Nematalla, Asaad S.
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060814	A2	20010823	WO 2001-US4813	20010215
WO 2001060814	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002156292	A1	20021024	US 2001-783264	20010215
US 6573293	B2	20030603		
EP 1255752	A2	20021113	EP 2001-914376	20010215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003523340	T2	20030805	JP 2001-560198	20010215
NO 2002003831	A	20021015	NO 2002-3831	20020813
BG 107078	A	20030430	BG 2002-107078	20020910

PRIORITY APPLN. INFO.:
US 2000-182710P P 20000215
US 2000-216422P P 20000706
US 2000-243532P P 20001027
WO 2001-US4813 W 20010215

OTHER SOURCE(S): MARPAT 135:195497
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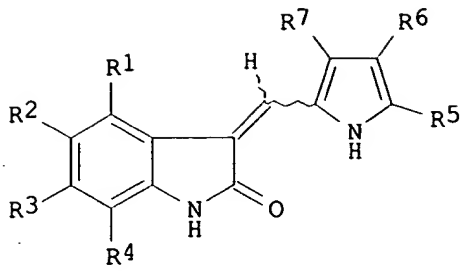

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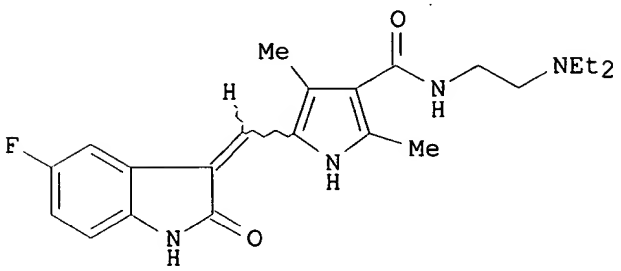

II

AB The title compds. (I) [wherein R1 = H, halo, (cyclo)alkyl, (hetero)aryl, heteroalicyclic, OH, alkoxy, acyl, (un)substituted amino or carbamoyl, etc.; R2 = H, halo, alkyl, trihalomethyl, OH, alkoxy, CN, (hetero)aryl, (un)substituted amino, acyl(amino), or sulfamoyl, etc.; R3 = H, halo, alkyl, trihalomethyl, OH, alkoxy, (hetero)aryl; (un)substituted acyl, (acyl)amino, sulfamoyl, or alkylsulfonyl, etc.; R4 = H, halo, alkyl, OH, alkoxy, or (un)substituted amino; R5 and R6 = independently H, alkyl, or acyl; R7 = H, alkyl, (hetero)aryl, or acyl; and their pharmaceutically acceptable salts] were prepd. as protein kinase modulators for the treatment of cellular disorders such as cancer. For example, 5-fluoro-1,3-dihydroindol-2-one was condensed with 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide to give II (55%). II exhibited comparable activity against Flk-1 and PDGFR.beta. and inhibited PDGF-dependent receptor phosphorylation in cells with an IC50 value of approx. 0.03 .mu.M. In efficacy expts. against various cancers in mice, II was well tolerated at 80 mg/kg/day, even when dosed continuously for more than 100 days.

L3 ANSWER 22 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:507531 HCAPLUS
DOCUMENT NUMBER: **135:107247**
TITLE: Preparation of 3-heteroarylidenyl-2-indolinone compounds for modulating protein kinase activity and for use in cancer chemotherapy
INVENTOR(S): Langecker, Peter J.; Shawver, Laura K.; Tang, Peng C.; Sun, Li
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049287	A1	20010712	WO 2000-US18058	20000630
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2000038519	A1	20000706	WO 1999-US31232	19991230
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003073837	A1	20030417	US 1999-476232	19991230
EP 1259234	A1	20021127	EP 2000-943334	20000630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.:

US 1999-476232	A	19991230
WO 1999-US31232	A	19991230
US 2000-569545	A	20000512
US 1998-114313P	P	19981231
WO 2000-US18058	W	20000630

OTHER SOURCE(S): MARPAT 135:107247

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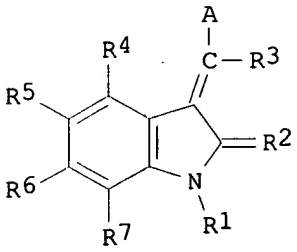


I

AB The present invention relates to 3-heteroarylidenyl-2-indolinone compds. [I; R1 = H, alkyl; R2 = O, S; R3 = H; R4 , R5, R6, R7 = H, alkyl, alkoxy, aryl, aryloxy, alkaryloxy, halo, trihalomethyl, S(O)R, SO2NRR', SO3R, SR, NO2, NRR', OH, cyano, COR, O2CR, (CH2)nCO2R, CONRR'; A = a five membered heteroaryl selected from (un)substituted thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, etc.; n = 0-3; R, R' = H, alkyl, aryl] or physiol. acceptable salts or prodrugs thereof are prepd. These compds. modulate the enzymic activity of protein kinases such as receptor protein tyrosine kinase, cellular tyrosine kinase, and serine threonine kinase and therefore are expected to be useful in the prevention and

treatment of protein kinase related cellular disorders such as cancer. Furthermore, these compds. are expected to enhance the efficacy of other chemotherapeutic agents, in particular, fluorinated pyrimidines, in the treatment of cancer. In a cellular-based assay for inhibiting the receptor phosphorylation, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-2-indolinone (II) inhibited Flk-1-autophosphorylation with IC50 of .apprx.1 .mu.M. II in vitro inhibited proliferation of **endothelial** cells induced by **VEGF** with IC50 of .apprx.0.07 .mu.M. Although II in vitro had no direct inhibitory effect on a variety of tumor cell lines at concn. up to 50 .mu.M, it in vivo demonstrated a significant suppression of tumor growth against a broad spectrum of tumor types s.c. implanted into immunocompromised mice and whose growth are driven by various growth factors such as PDGF, EGF, and Her2.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

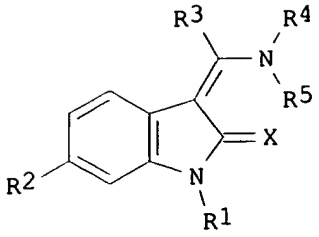
L3 ANSWER 23 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:283925 HCAPLUS
DOCUMENT NUMBER: **134:311105**
TITLE: Prepn. of substituted aminomethyleneindolinone inhibitors of tyrosine receptor kinases and CDK/cyclin kinases as antitumor agents and inhibitors of cell proliferation
INVENTOR(S): Heckel, Armin; Roth, Gerald Juergen; Walter, Rainer; Van Meel, Jacobus; Redemann, Norbert; Tontsch-Grunt, Ulrike; Spevak, Walter; Hilberg, Frank
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 282 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027081	A1	20010419	WO 2000-EP9867	20001009
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19949208	A1	20010419	DE 1999-19949208	19991013
DE 10042696	A1	20020314	DE 2000-10042696	20000831
BR 2000014735	A	20020716	BR 2000-14735	20001009
EP 1224170	A1	20020724	EP 2000-971347	20001009
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003511441	T2	20030325	JP 2001-530102	20001009
EE 200200197	A	20030616	EE 2002-197	20001009
BG 106587	A	20030131	BG 2002-106587	20020405
NO 2002001719	A	20020411	NO 2002-1719	20020411

PRIORITY APPLN. INFO.: DE 1999-19949208 A 19991013
DE 2000-10042696 A 20000831
WO 2000-EP9867 W 20001009

OTHER SOURCE(S): MARPAT 134:311105

GI



I

AB The invention relates to the prepn. of substituted (Z)-aminomethyleneindolines I [wherein X = O or S; R1 = H, C1-4 alkoxycarbonyl, C2-4 alkanoyl; R2 = HO2C, C1-6 alkoxycarbonyl, C4-7 cycloalkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, or alkyl-substituted aminocarbonyl; R3 = H, C1-6 alkyl, C3-7 cycloalkyl, CF3, heteroaryl, or (un)substituted Ph or naphthyl; R4 and R5 = independently C3-7 cycloalkyl, monosubstituted phenyl] isomers and salts thereof as receptor tyrosine kinase and cyclin/CDK complex inhibitors for the treatment of **endothelial** cells and tumor cell proliferation. For example, 1-acetyl-6-ethoxycarbonyl-3-(ethoxyphenylmethylene)-2-indolinone and N-(4-aminophenyl)-N-(3-dimethylaminopropyl)acetamide were stirred together in DMF at 100.degree. for 3h followed by addn. of piperidine to give I (X = O; R1 = H; R2 = EtO2C; R3 = EtO; R4 = (Me2NCH2CH2CH2)N(Ac)C6H4; R5 = H). I inhibited the proliferation of **endothelial** cells with an IC50 of 0.003 .mu.M.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

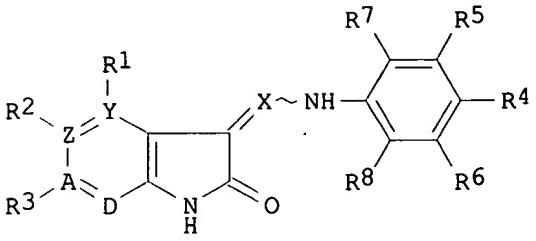
L3 ANSWER 24 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:688216 HCAPLUS
DOCUMENT NUMBER: **133:266726**
TITLE: Preparation of 3-(anilinomethylene)oxindoles and analogs as protein tyrosine kinase and protein serine/threonine kinase inhibitors
INVENTOR(S): Glennon, Kimberley Caroline; Kuyper, Lee Frederick; Lackey, Karen Elizabeth; McNutt, Robert Walton, Jr.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 189 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056710	A1	20000928	WO 2000-US5057	20000228

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1165514 A1 20020102 EP 2000-913643 20000228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
US 6350747 B1 20020226 US 2000-514528 20000228
JP 2002540097 T2 20021126 JP 2000-606572 20000228
US 6498176 B1 20021224 US 2001-914063 20010822
US 2002099071 A1 20020725 US 2001-966318 20010927
PRIORITY APPLN. INFO.: GB 1999-4933 A 19990304
US 2000-514528 A3 20000228
WO 2000-US5057 W 20000228
OTHER SOURCE(S): MARPAT 133:266726
GI



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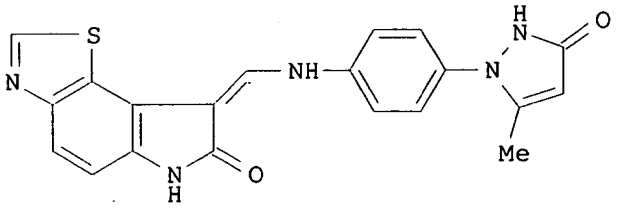


II

AB The title compds. (I) [wherein X = N, CH, CCF3, or C(aliph.); Y, Z, A, and D = C or N, and the no. of N .ltoreq. 1; R1 = H, aliph., SH, hydroxy(aliph.), aryl(aliph.), cycloalkyl(aliph.), heterocyclyl(aliph.), (un)substituted NH2, CONH2, or SO2NH2, alkoxycarbonyl, halo, CN, or NO2; R2 = H, aliph., hydroxyimino aliph., alkoxy(carbonyl), hydroxyaliph., aryl(oxycarbonyl), heterocyclyl, (un)substituted CONH2, NH2, or SO2NH2, halo, OH, NO2, aliph. sulfonyl, etc.; or R1 and R2 are joined to form an (un)substituted fused heterocyclic ring; R3 = H, aliph., hydroxy(aliph.), (un)substituted NH2, CONH2, or SO2NH2, alkoxy, aryl(oxy), hydroxyaryl, (hydroxy)heterocyclyl, heterocyclyloxy, or halo; or R2 and R3 are joined to form an (un)substituted fused heterocyclic ring; R4 = SO3H, (aliph.)sulfonyl(aliph.), (un)substituted SO2NH2, NH2, CONH2, etc.; R5 = H; or R4 and R5 are joined to form an (un)substituted fused heterocyclic ring] were prepd. via std. synthetic methods and soln. phase library techniques as vascular **endothelial** growth factor receptor type 2 (**VEGFR**-2), cyclin dependent kinase 2 (CDK2), tyrosine kinase Tie-2 receptor, and colony-stimulating factor 1 receptor kinase (c-fms) inhibitors. For example, a mixt. of 8-dimethylaminomethylene-6,8-dihydro-1-thia-3,6-diaza-as-indacene-7-one (prepn. given) and 2-(4-aminophenyl)-3-methylpyrazolin-5-one in abs. EtOH was heated with stirring at 90.degree.C for 16 h to give (Z)-II (83%). In substrate phosphorylation assays, II inhibited **VEGFR**-2 and CDK2 with IC50 values of 1-10 .mu.M and 11-50 .mu.M, resp. I are useful as therapeutic agents in disease states

alleviated by the inhibition or antagonism of protein kinase activated signalling pathways in general, and in particular in the pathol. processes which involve aberrant cellular proliferation, such as tumor growth, restenosis, atherosclerosis, and thrombosis. I are particularly useful for suppressing tumor growth by inhibiting tumor-related **angiogenesis**.

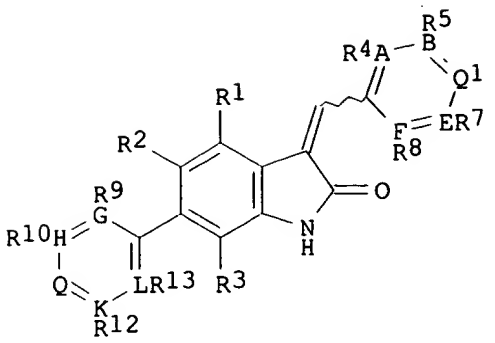
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:688215 HCAPLUS
DOCUMENT NUMBER: **133:252306**
TITLE: Preparation of indolinones as protein kinase inhibitors.
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald; Miller, Todd Anthony; Shirazian, Shahrzad; Wei, Chung Chen; Harris, G. Davis; Xiaoyuan, Li; Liang, Congxin
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 245 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056709	A1	20000928	WO 2000-US7704	20000322
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165513	A1	20020102	EP 2000-916622	20000322
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002540096	T2	20021126	JP 2000-606571	20000322

PRIORITY APPLN. INFO.:
US 1999-125945P P 19990324
US 1999-127863P P 19990405
US 1999-131192P P 19990426
US 1999-132243P P 19990503
WO 2000-US7704 W 20000322

OTHER SOURCE(S): MARPAT 133:252306
GI



I

AB Title compds., e.g. [I; m, n = 0, 1; Q = (JR11)m; Q1 = (DR6)n; when n = 1, then A, B, D, E, F = C, N; .ltoreq.3 of A, B, D, E, F = N; when m = 1, then G, H, J, K, L = C, N; .gtoreq.1 and .ltoreq.3 of G, H, J, K, L = N; when n = 0, then A = C, N, B, F = C, N, NH, O, S; E = C, N, O, S; when m = O, then G = C, N, H, K, l = C, N, NH, O, S; R1-R13 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, OH, alkoxy, SH, alkylthiol, aryloxy, amino, etc.; R4R5 or R5R6 or R6R7 or R7R8 = atoms to form a 5-6 membered (hetero)aryl ring; with addnl. provisos], were prepd. Thus, 6-pyridin-3-yl-1,3-dihydroindol-2-one (prepn. given), 4-methoxy-3-thien-2-ylbenzaldehyde, and piperidine were refluxed overnight in EtOH to give 15% 3-(4-methoxy-3-thien-2-ylbenzylidene)-6-pyridin-3-yl-1,3-dihydroindol-2-one. Tested title compds. inhibited HER2 kinase with IC50 = 16.4 .mu.M to .gtoreq.100 .mu.M.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:622463 HCAPLUS

DOCUMENT NUMBER: **133:217719**

TITLE: 3-(Cyclohexanoheteroarylidenyl)-2-indolinone protein tyrosine kinase inhibitors, and their therapeutic use

INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Blake, Robert A.

PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: U.S., 61 pp., Cont. -in-part of U.S. Ser. No. 99,842. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6114371	A	20000905	US 1998-190970	19981112
US 6130238	A	20001010	US 1998-99842	19980619
US 2002183370	A1	20021205	US 2001-29946	20011231
US 6579897	B2	20030617		

PRIORITY APPLN. INFO.:

US 1997-50977P	P	19970620
US 1997-59384P	P	19970919
US 1998-99842	A2	19980619
US 1997-50413P	P	19970620
US 1997-59544P	P	19970919
US 1998-99721	A1	19980619
US 2000-482198	A3	20000112

OTHER SOURCE(S): CASREACT 133:217719; MARPAT 133:217719
AB 3-(Cyclohexano-heteroarylidenyl)-2-indolinone compds., and physiol. acceptable salts and prodrugs thereof, are disclosed which are expected to modulate the activity of protein tyrosine kinases and therefore to be useful in the prevention and treatment of protein tyrosine kinase-related cellular disorders (cancer, arthritis, restenosis, etc.).
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:456819 HCAPLUS
DOCUMENT NUMBER: **133:84238**
TITLE: 3-heteroarylidenyl-2-indolinone compounds for modulating protein kinase activity and for use in cancer chemotherapy
INVENTOR(S): Langecker, Peter J.; Shawver, Laura Kay; Tang, Peng Cho; Sun, Li
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038519	A1	20000706	WO 1999-US31232	19991230
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2357042	AA	20000706	CA 1999-2357042	19991230
BR 9916735	A	20010925	BR 1999-16735	19991230
EP 1139754	A1	20011010	EP 1999-966725	19991230
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002533360	T2	20021008	JP 2000-590484	19991230
AU 760964	B2	20030522	AU 2000-22215	19991230
WO 2001049287	A1	20010712	WO 2000-US18058	20000630
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1259234	A1	20021127	EP 2000-943334	20000630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.:

US 1998-114313P	P	19981231
US 1999-476232	A	19991230
WO 1999-US31232	W	19991230
US 2000-569545	A	20000512

WO 2000-US18058 W 20000630

OTHER SOURCE(S): MARPAT 133:84238

AB 3-Heteroarylidenyl-2-indolinone compds. are provided that modulate the enzymic activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase-related cellular disorders, e.g. cancer. Furthermore, these compds. are expected to enhance the efficacy of other chemotherapeutic agents, in particular, fluorinated pyrimidines, in the treatment of cancer.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:117197 HCAPLUS

DOCUMENT NUMBER: **132:166123**

TITLE: 3-Methylidenyl-2-indolinone modulators of protein kinase

INVENTOR(S): Tang, Peng Cho; Sun, Li; Miller, Todd Anthony; Liang, Congxin; Tran, Ngoc My; Nguyen, Anh Thi; Nematalla, Asaad

PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: PCT Int. Appl., 347 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008202	A2	20000217	WO 1999-US17845	19990804
WO 2000008202	A3	20000518		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9954684	A1	20000228	AU 1999-54684	19990804
JP 2002522452	T2	20020723	JP 2000-563824	19990804
US 6531502	B1	20030311	US 2001-762198	20010205
US 2002183364	A1	20021205	US 2001-13944	20011213

PRIORITY APPLN. INFO.:

US 1998-129256	A	19980804
US 1998-95470P	P	19980805
US 1998-102178P	P	19980928
US 1999-116107P	P	19990115
US 1998-72023P	P	19980121
WO 1999-US17845	W	19990804
US 1999-407164	A1	19990928

OTHER SOURCE(S): MARPAT 132:166123

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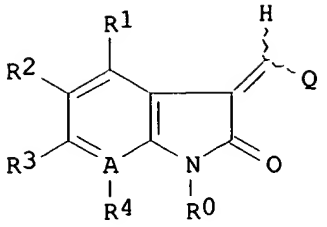

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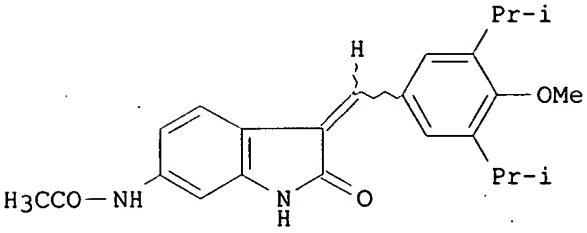


II

AB The title compds. (I) [wherein A = C or N; Q = substituted Ph, pyrrolyl, or indolyl; R0 = H, alkyl, C(O)R19, or C(O)OR19; R1 = H, (un)substituted alkyl, alkoxy, halo, aryl, (CH2)nOC(O)R19, or C(O)NR19; R2 = H, (cyclo)alkyl, (hetero)aryl, heteroalicyclic, trihalomethyl, alkoxy, halo, sulfamido, C(O)OR19, C(O)R19, NHC(O)OR19, (un)substituted amino, etc.; R3 = H, alkyl, trihalomethyl, alkoxy, aryl(oxy), heteroaryl, heteroalicyclic, OH, halo, sulfamido, C(O)R19, (un)substituted amino, etc.; R4 = H, alkyl, alkoxy, or halo; R19 = H, (cyclo)alkyl, alkenyl, alkynyl, or aryl; n = 1-4] were prepd. as modulators of the activity of receptor tyrosine kinases (RTKs), non-receptor protein tyrosine kinases (CTKs), and serine/threonine protein tyrosine kinases (STKs). Examples include over 200 syntheses and data from seventeen bioassays. For instance, II was prepd. by a 3-step sequence involving: (1) cyclization and redn. of 2,4-dinitrophenylacetic acid with SnCl2.2H2O in EtOH to form 6-amino-2-oxindole, (2) amidation with AcCl in CH2Cl2, and (3) condensation of the amide with 3,5-diisopropyl-4-methoxybenzaldehyde. II was tested for HER-2 kinase activity (IC50 = 6.4 .mu.M), cellular proliferation activity as measured by the incorporation of bromodeoxyuridine (BrdU) driven by HER-2 (IC50 = 9.1 .mu.M) or EGF (IC50 = 11 .mu.M), and antitumor activity as measured by growth of SKOV3 ovarian carcinoma cells (IC50 = 2.6 .mu.M) or A431 human epidermoid carcinoma cells (IC50 = 2.2 .mu.M). The invention compds. are expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer, diabetes, hepatic cirrhosis, cardiovascular disease, and immunol. disease.

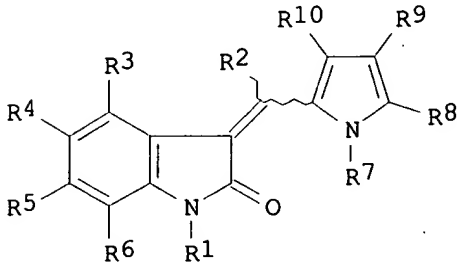
L3 ANSWER 29 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:764021 HCAPLUS
DOCUMENT NUMBER: **132:12257**
TITLE: Preparation of pyrrole substituted 2-indolinone protein kinase inhibitors
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 240 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9961422	A1	19991202	WO 1999-US12069	19990528
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2314156	AA	19991202	CA 1999-2314156	19990528
AU 9944102	A1	19991213	AU 1999-44102	19990528
AU 759226	B2	20030410		
EP 1082305	A1	20010314	EP 1999-927120	19990528
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
BR 9910792	A	20020129	BR 1999-10792	19990528
US 6395734	B1	20020528	US 1999-322297	19990528
JP 2002516310	T2	20020604	JP 2000-550828	19990528
NO 2000005916	A	20010129	NO 2000-5916	20001122
US 2003105151	A1	20030605	US 2002-81147	20020225

PRIORITY APPLN. INFO.:
US 1998-87310P P 19980529
US 1999-116106P P 19990115
US 1999-322297 A1 19990528
WO 1999-US12069 W 19990528

OTHER SOURCE(S): MARPAT 132:12257
GI



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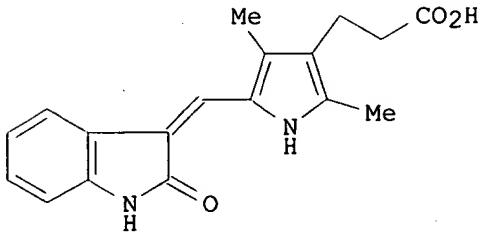


II

AB The present invention relates to 5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrol-3-ylalkanoic acid derivs. (I) [where R1 and R7 =

independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl, OH, alkoxy, carboxy, acetyl, (thio)amido, (trihalomethane)sulfonyl, etc.; R2 = H, halo, (cyclo)alkyl, (hetero)aryl, or heteroalicyclic; R3, R4, R5, R6, R8, R9, R10 = independently H, (cyclo)alkyl, trihaloalkyl, alkenyl, alkynyl, (hetero)aryl(oxy), heteroalicyclic, OH, alkoxy, SH, alkylthio, arylthio, sulfinyl, sulfonyl, sulfonamido , carbonyl, carboxy, amido, CN, NO2, halo, (thio)carbamyl, (un)substituted amino, etc.] which modulate the activity of protein kinases and are useful in the prevention and treatment of protein kinase related cellular disorders, such as cancer. Thus, 2,4-dimethyl-5-ethoxycarbonyl-3-(2-ethoxycarbonylethyl)pyrrole was deprotected using NaOH to form 3-(2-carboxyethyl)-2,4-dimethylpyrrole (100%) and the product C-5 formylated (two methods given for 86% and 90% yield, resp.). Reaction with 2-oxindole in EtOH and pyrrolidine or in aq. NaOH yielded II (88% and 91%, resp.), which reduced the av. size of C6 human glioma and melanoma tumors s.c. implanted in mice by 80-85%. II, when administered orally, demonstrated notably superior efficacy compared to structurally similar analogs.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:626172 HCAPLUS
DOCUMENT NUMBER: **131:257441**
TITLE: Heterocyclic families of compounds [tricyclic-based indolinones and pyrazolecarboxylic acid amides] for the modulation of tyrosine protein kinase
INVENTOR(S): Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang, Congxin; McMahon, Gerald; Mohammadi, Moosa; Schlessinger, Joseph; Shawver, Laura K.; Sun, Li; Tang, Peng C.; Ullrich, Axel
PATENT ASSIGNEE(S): Sugen, Inc., USA; New York University; Max-Planck Institut fur Biochemie
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948868	A2	19990930	WO 1999-US6468	19990326
WO 9948868	A3	20000224		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2325935	AA	19990930	CA 1999-2325935	19990326
AU 9933635	A1	19991018	AU 1999-33635	19990326
EP 1066257	A2	20010110	EP 1999-915018	19990326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002507598	T2	20020312	JP 2000-537851	19990326
US 6514981	B1	20030204	US 1999-283657	19990401
US 2002022626	A1	20020221	US 2000-617529	20000713

US 2003108946	A1	20030612	US 2002-76621		20020219
PRIORITY APPLN. INFO.:			US 1998-79713P	P	19980326
			US 1998-80422P	P	19980402
			US 1998-81792P	P	19980415
			US 1998-82056P	P	19980416
			US 1998-89397P	P	19980615
			US 1998-89521P	P	19980616
			US 1998-98783P	P	19980901
			US 1997-915366	A3	19970820
			WO 1999-US6468	W	19990326
			US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 131:257441
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

L3 ANSWER 31 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	1999:222914 HCAPLUS
DOCUMENT NUMBER:	**130:267341**
TITLE:	Preparation of oxindoles as protein tyrosine kinase and protein serine/threonine kinase inhibitors.
INVENTOR(S):	Davis, Stephen Thomas; Dickerson, Scott Howard; Frye, Stephen Vernon; Harris, Philip Anthony; Hunter, Robert Neil, III; Kuyper, Lee Frederick; Lackey, Karey Elizabeth; Luzzio, Michael Joseph; Veal, James Marvin; Walker, Duncan Herrick
PATENT ASSIGNEE(S):	Glaxo Group Limited, UK
SOURCE:	PCT Int. Appl., 133 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9915500	A1	19990401	WO 1998-EP5559	19980903

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

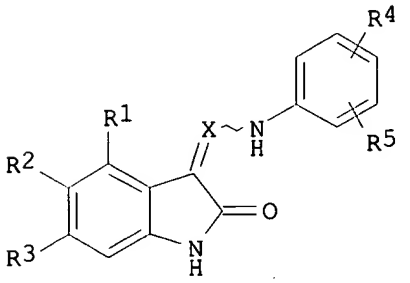
CA 2302572	AA	19990401	CA 1998-2302572	19980903	
AU 9897407	A1	19990412	AU 1998-97407	19980903	
AU 747506	B2	20020516			
ZA 9808078	A	20000322	ZA 1998-8078	19980903	
EP 1009738	A1	20000621	EP 1998-951342	19980903	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 9812048	A	20000926	BR 1998-12048	19980903	
EE 200000117	A	20001215	EE 2000-20000011719980903		
JP 2001517652	T2	20011009	JP 2000-512809	19980903	
US 6369086	B1	20020409	US 1999-262351	19990304	
MX 200002254	A	20001030	MX 2000-2254	20000303	
US 6387919	B1	20020514	US 2000-486960	20000606	
US 2003004351	A1	20030102	US 2001-924431	20010808	
US 6541503	B2	20030401			
US 2003069430	A1	20030410	US 2001-999331	20011130	

PRIORITY APPLN. INFO.:

GB 1997-18913	A	19970905
WO 1998-EP5559	W	19980903
US 1999-262351	A3	19990304
US 2000-486960	A3	20000606

OTHER SOURCE(S): MARPAT 130:267341

GI



I

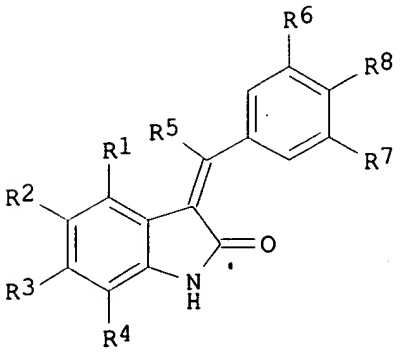
AB Title compds. [I; X = N, CH, CCF3, CA; A = aliphatyl; R1 = H, SH, OH, HOA, heterocyclyl, AHN, A2N, A2NCO, halo, cyano, NO2, etc.; R2 = H, A, HONA, alkoxy, HOA, heterocyclyl, A2NSO2, halo, NO2, OH, ASO2, etc.; R3 = H, A, OH, HOA, A2N, aryl, aryloxy, hydroxyaryl, heterocyclyl, hydroxyheterocyclyl, etc.; R4 = SO3H, SO2A, A2N, A2NCO, heterocyclylamino, heterocyclylsulfonyl, etc.; R5 = H; R1R2, R4R5 = fused ring], were prepd. Thus, (Z)-N-(3-hydroxy-2,2-dimethylpropyl)-4-[(7-oxo-6,7-dihydro-1-thia-3,6-diaza-as-indacen-8-ylidenemethyl)amino]benzenesulfonamide [prepd. from 8-ethoxymethylene-6,8-dihydro-1-thia-3,6-diaza-as-indacen-7-one and 4-amino-N-(3-hydroxy-2,2-dimethylpropyl)benzenesulfonamide] inhibited protein kinases CDK1, CDK2, and UL97 with IC50 = 1-10 nM.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 32 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:166598 HCAPLUS
DOCUMENT NUMBER: **130:209599**
TITLE: Preparation of benzylidene-1,3-dihydroindol-2-ones as receptor tyrosine kinase inhibitors.
INVENTOR(S): McNutt, Robert Walton, Jr.; Jung, David Kendall; Harris, Philip Anthony; Hunter, Robert Neil, III; Veal, James Marvin; Dickerson, Scott; Lackey, Karen Elizabeth; Peel, Michael Robert
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 144 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910325	A1	19990304	WO 1998-EP4844	19980804
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9891584	A1	19990316	AU 1998-91584	19980804
EP 1003721	A1	20000531	EP 1998-943832	19980804
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002514228	T2	20020514	JP 1999-513839	19980804
ZA 9807037	A	20000207	ZA 1998-7037	19980805
US 6268391	B1	20010731	US 2000-446586	20000407

PRIORITY APPLN. INFO.: GB 1997-16557 A 19970806
WO 1998-EP4844 W 19980804
OTHER SOURCE(S): MARPAT 130:209599
GI



I

AB Title compds. [I; R1 = H; R1R2 = fused 5-10 membered aryl, heteroaryl, heterocyclyl; R2, R3 = H, HET, aryl, aliphatyl, cyano, NO2, halo, R10,

OR10, SR10, SOR10, SO2R10, NR10R11, etc.; R4 = H, halo, NO2, cyano; R5 = H, (substituted) aliphatyl; R6, R7 = halo, cyano, NO2, CONR10R11, SO2NR10R11, NR10R11, OR11; R8 = OH, NHSO2R12, NHCOCF3; R10 = H, halo, (substituted) aliphatyl, aryl, HET; R11 = H, R10; R12 = H, (substituted) aliphatyl, HET; HET = benzofuryl, benzoxazolyl, dioxanyl, dithianyl, dithiazinyl, furyl, imidazolyl, indolyl, indazolyl, morpholinyl, tetrazolyl, pyrrolyl, quinolinyl, triazinyl, tetrahydrofuryl, etc.], were prepd. for treatment of tumor growth, preventing organ transplant rejection, healing chronic wounds, etc. (no data). Thus, 5-(2-methylthiazol-4-yl)-1,3-dihydroindol-2-one hydrochloride (prepn. given) was stirred with 3,5-dibromo-4-hydroxybenzaldehyde in AcOH/aq. HCl to give 64% 3-(3,5-dibromo-4-hydroxybenzylidene)-5-(2-methylthiazol-4-yl)-1,3-dihydroindol-2-one.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

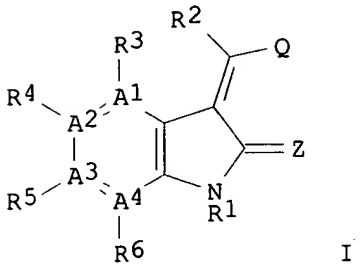
L3 ANSWER 33 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:747592 HCAPLUS
DOCUMENT NUMBER: **130:3771**
TITLE: Preparation of 3-(hetero)arylmethylidene-2-indolinone derivatives as modulators of protein kinase activity for use in treating cancer.
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Shawver, Laura Kay; Hirth, Klaus Peter
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850356	A1	19981112	WO 1998-US9017	19980507
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9876842	A1	19981127	AU 1998-76842	19980507
EP 984930	A1	20000315	EP 1998-924746	19980507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002511852	T2	20020416	JP 1998-548319	19980507
US 2003158215	A1	20030821	US 1998-96014	19980610
US 6051593	A	20000418	US 1998-99721	19980619
US 6313158	B1	20011106	US 1998-100854	19980619
US 6133305	A	20001017	US 1998-161046	19980925
US 2001056094	A1	20011227	US 2000-482198	20000112
US 2001007033	A1	20010705	US 2000-516948	20000301
US 2002026053	A1	20020228	US 2001-916331	20010730
US 6506763	B2	20030114		
US 2002058661	A1	20020516	US 2001-948106	20010907
US 2002183370	A1	20021205	US 2001-29946	20011231
US 6579897	B2	20030617		

PRIORITY APPLN. INFO.: US 1997-45838P P 19970507

US 1997-46868P	P	19970508
US 1997-49324P	P	19970611
US 1997-50412P	P	19970620
US 1997-50413P	P	19970620
US 1997-50977P	P	19970620
US 1997-59336P	P	19970919
US 1997-59381P	P	19970919
US 1997-59384P	P	19970919
US 1997-59544P	P	19970919
US 1997-59677P	P	19970919
US 1997-59971P	P	19970925
US 1997-60194P	P	19970926
WO 1998-US9017	W	19980507
US 1998-100854	A3	19980619
US 1998-99721	A1	19980619
US 1998-161046	A3	19980925
US 2000-482198	A3	20000112
US 2000-516948	B1	20000301

OTHER SOURCE(S): MARPAT 130:3771
GI



I

AB Title compds. [I; A1-A4 = C, N; when any of A1-A4 = N, then the corresponding R3-R6 = null; R1 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, trihalomethylcarbonyl, OH, CO2H, trihalomethylsulfonyl, etc.; R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclyl, halo; R3-R6 = H, alkyl, trihalomethyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, OH, SH, alkoxy, aryloxy, amino, phosphonyl, guanidinyl, NO2, halo, (iso)cyanato, etc.; R3R4 or R4R5 or R5R6 = cycloalkyl, aryl, heteroaryl, heteroalicyclyl, OCH2O, OCH2CH2O; Q = specified (substituted) (hetero)aryl; Z = O, S], were prepd. Thus, 3-(4-imidazolylmethylidenyl)-4,6-dimethyl-2-indolinone inhibited CDK2 with IC50 = <0.78 .mu.M.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 34 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:151222 HCAPLUS
DOCUMENT NUMBER: **128:164361**
TITLE: Crystal structures of a protein tyrosine kinase
INVENTOR(S): Mohammadi, Moosa; Li, Sun; Liang, Congxin; Schlessinger, Joseph; Hubbard, Stevan R.; McMahon, Gerald; Tang, Peng C.
PATENT ASSIGNEE(S): Sugen, Inc., USA; Mohammadi, Moosa; Li, Sun; Liang, Congxin; Schlessinger, Joseph; Hubbard, Stevan R.; McMahon, Gerald; Tang, Peng C.
SOURCE: PCT Int. Appl., 493 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807835	A2	19980226	WO 1997-US14885	19970821
WO 9807835	A3	19981001		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5942428	A	19990824	US 1996-701191	19960821
AU 9741603	A1	19980306	AU 1997-41603	19970821
EP 931152	A2	19990728	EP 1997-939534	19970821
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001514484	T2	20010911	JP 1998-511036	19970821

PRIORITY APPLN. INFO.: US 1996-701191 A 19960821
US 1996-34168P P 19961219
WO 1997-US14885 W 19970821

OTHER SOURCE(S): MARPAT 128:164361

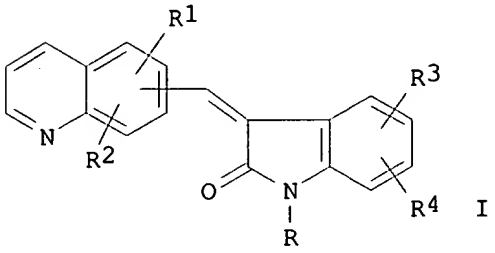
AB The present invention relates to the 3-dimensional structures of a protein tyrosine kinase optionally complexed with one or more compds. Thus, a 310-amino acid fragment fibroblast growth factor receptor 1 (residues 456-765, FGFR1) was recombinantly prepd. contg. the amino acid substitutions Cys488.fwdarw.Ala, Cys584.fwdarw.Ser, and Leu457.fwdarw.Val, and an addnl. 5 residues (Ser-Ala-Ala-Gly-Thr) at the N-terminus. X-ray crystallog. yielded the at. structural coordinates of cryst. FGFR1 and its complexes with adenylyl diphosphonate, 3-[(3-(2-carboxyethyl)-4-methylpyrrol-5-yl)methylene]-2-indolinone, or 3-[4-(4-formylpiperazine-1-yl)benzylidenyl]-2-indolinone. Two forms of cryst. FGFR1 were obtained: one form (designated C2-A form) with unit cell dimensions of a = 208.3, b = 57.2, c = 65.5.ANG. and .beta. = 107.2.degree., and another C2-B form with dimensions a = 211.6, b = 51.3, c = 66.1.ANG. and .beta. = 107.7.degree.. The overall structure of FGFR1 is bi-lobate. The N-terminal lobe of FGFR1 spans amino acid residues 456-567 and comprises a curled .beta.-sheet of five antiparallel strands and one .alpha.-helix. The C-terminal lobe spans amino acid residues 568-765 and comprises two .beta.-strands and seven .alpha.-helixes. The at. coordinates that define the structures of the protein tyrosine kinase and any of the compds. bound to it are pertinent to methods for detg. the 3-dimensional structures of protein tyrosine kinases with unknown structure and to methods that identify modulators of protein tyrosine kinase functions.

L3 ANSWER 35 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:1471 HCAPLUS
DOCUMENT NUMBER: **128:61437**
TITLE: Preparation of substituted quinolylmethylenoxoindole analogs as tyrosine kinase inhibitors
INVENTOR(S): Battistini, Carlo; Ermoli, Antonella; Vioglio, Sergio; Buzzetti, Franco; Ballinari, Dario
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy
SOURCE: PCT Int. Appl., 51 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9746551	A1	19971211	WO 1997-EP2673	19970515
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 876365	A1	19981111	EP 1997-927035	19970515
R: DE, GB, IT				
JP 11510823	T2	19990921	JP 1997-500166	19970515
US 5905149	A	19990518	US 1998-983516	19980129

PRIORITY APPLN. INFO.: GB 1996-11797 19960606
WO 1997-EP2673 19970515
OTHER SOURCE(S): MARPAT 128:61437
GI



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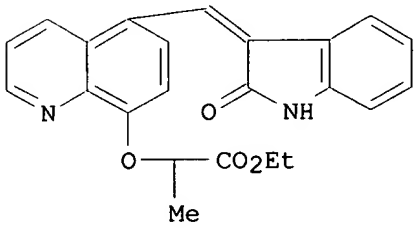


II

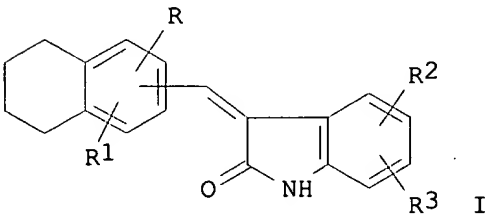
AB The title compds. [I; R1-R4 = X(CH2)mNH2, X(CH2)mNR5R6, etc.; R = H, (CH2)nCOR7, etc.; n = 1-4; m = 2-4; R5, R6 = H, C1-6 alkyl; R7 = (un)substituted amino acids, etc.] and the pharmaceutically acceptable salts thereof are prepd. I, possessing tyrosine kinase inhibitory activity, are useful as immunomodulating agents, and antimetastatic and anticancer agents, or in the control of **angiogenesis** and atheromatous plaque, and treatment of Alzheimer's disease. Thus, 8-hydroxyquinoline-5-carbaldehyde was reacted with 2-oxoindole in the presence of piperidine and then reacted with MeCHBrCO2OEt in the presence of Bu4NF to give the title compd. (II), which showed IC50 of 39.5 .mu.M against K562 cell growth in vivo. A formulation contg. I were also prepd.

L3 ANSWER 36 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:805721 HCAPLUS

DOCUMENT NUMBER: **128:61424**
TITLE: Preparation of substituted tetralinylmethylen-2-oxoindole analogs as tyrosine kinase inhibitors
INVENTOR(S): Battistini, Carlo; Ermoli, Antonella; Vioglio, Sergio; Buzzetti, Franco; Ballinari, Dario
PATENT ASSIGNEE(S): Pharmacia & Upjohn, S.p.A., Italy
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745409	A1	19971204	WO 1997-EP2672	19970515
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 853614	A1	19980722	EP 1997-927034	19970515
EP 853614	B1	20011004		
R: DE, GB, IT				
JP 11510822	T2	19990921	JP 1997-541580	19970515
US 6147073	A	20001114	US 1998-981473	19980112

PRIORITY APPLN. INFO.: GB 1996-10964 A 19960524
WO 1997-EP2672 W 19970515
OTHER SOURCE(S): MARPAT 128:61424
GI



I

AB The title compds. [I; R, R1-R3 = X(CH2)mNH2, X(CH2)mNR4R5, etc.; X = O, S, NH, etc.; m = 2-4; R4, R5 = H, C1-6 alkyl, etc.] and pharmaceutically acceptable salts thereof are prepd. I, possessing tyrosine kinase inhibitory activity, are useful as antiproliferative, anti-metastatic, immunomodulating, and anticancer agents, or in the control of **angiogenesis** and in the treatment of Alzheimer's diseases. Thus, I (R = R1 = R3 = H, R2 = 5-NH2) (prepn. given) was reacted with N-tert-butoxycarbonyl-L-glutamic acid tert-Bu ester in the presence of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate and N-methylmorpholine, and then treated with CF3CO2H to give 40% I.CF3CO2H (R, R1, R3 = same as above, R2 = glutamylamino), which showed IC50 of 5.97 .mu.M against K562 cell growth in vivo. A formulation contg. I were prepd.

L3 ANSWER 37 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:140244 HCAPLUS
DOCUMENT NUMBER: **126:139901**
TITLE: Indolinone compounds capable of modulating tyrosine

kinase signal transduction
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640116	A1	19961219	WO 1996-US8903	19960605
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
AU 9660441	A1	19961230	AU 1996-60441	19960605
AU 706597	B2	19990617		
EP 769947	A1	19970502	EP 1996-918093	19960605
EP 769947	B1	20010502		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9606410	A	19971230	BR 1996-6410	19960605
JP 10504323	T2	19980428	JP 1996-501363	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
AT 200863	E	20010515	AT 1996-918093	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
NO 9605377	A	19970212	NO 1996-5377	19961213
HK 1011933	A1	20020118	HK 1998-113193	19981211
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
WO 1996-US8903	W	19960605
US 1997-915366	A3	19970820
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 126:139901

AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

L3 ANSWER 38 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:746204 HCAPLUS
DOCUMENT NUMBER: **126:18783**
TITLE: Substituted indolylmethylene-oxindole analogs as tyrosine kinase inhibitors
INVENTOR(S): Battistini, Carlo; Ballinari, Dario; Ermoli, Antonella; Penco, Sergio; Vioglio, Sergio
PATENT ASSIGNEE(S): Pharmacia S.P.A., Italy
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9632380	A1	19961017	WO 1996-EP1165	19960314
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 764152	A1	19970326	EP 1996-907500	19960314
EP 764152	B1	20020731		
R: DE, ES, FR, GB, IT, SE				
JP 10501821	T2	19980217	JP 1996-530667	19960314
ES 2181875	T3	20030301	ES 1996-907500	19960314
US 5849710	A	19981215	US 1996-750208	19961204

PRIORITY APPLN. INFO.: GB 1995-7298 A 19950407
WO 1996-EP1165 W 19960314
OTHER SOURCE(S): MARPAT 126:18783
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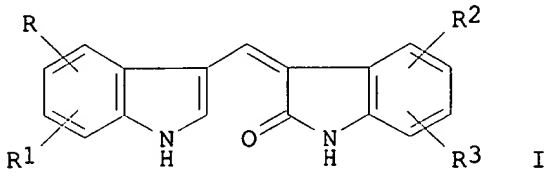

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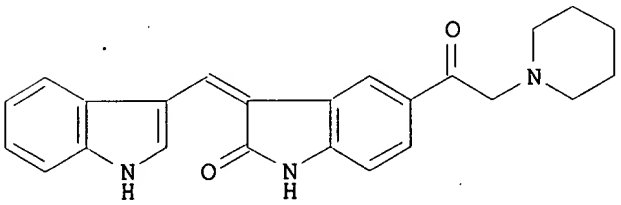

II

AB Indol-3-ylmethylene-2-oxindole derivs. I and their pharmaceutically acceptable salts are disclosed [wherein 1 or 2 of R, R1, R2, and R3 = X(CH2)mNH2, X(CH2)mNR4R5, X(CH2)mNHR6, NHC(:NH)NH2, NHC(:NH)NR4R5, NHC(:NH)NHR6, N:CHNH2, N:CHNR4R5, N:CHNHR6, X(CH2)mCOR7, CORa, COR8, YCOY'R9, NHR6, NHR10 group; remaining groups within R and R1-R3 = H, halo, amino, OH, alkyl, alkoxy, CO2H, alkoxycarbonyl, alkanoyloxy, cyano, NR4R5; X = O, S, NH; m = 1-4; 1 of R4 and R5 = H or alkyl, and other = alkyl; or NR4R5 forms satd. monoheterocycle; R6 = alkanoyl, 1- to 3-residue (un)substituted peptidyl; R7 = OH, amino, alkoxy, NR4R5; Ra = amino

terminus of 1- to 3-unit peptidyl; R8 = alkoxy, phenylalkoxy, (CH2)nNH2, (CH2)nNR4R5, (CH2)nNHR6; n = 1-2; Y, Y' = NH, O; R9 = Ph, alkyl, phenylalkyl; R10 = mono-, di- or trihydroxyalkyl]. I have tyrosine kinase inhibiting activity, and are useful as antiproliferative, antimetastatic, anticancer, antiatheromatous, anti-Alzheimer, and immunomodulating agents. For example, 2-indolinone reacted with BrCH2COBr and AlCl3 to give the 5-(2-bromoacetyl) deriv., which underwent amination with piperidine and then condensation with indole-3-carboxaldehyde, to give title compd. II (FCE 28484). In tests for inhibition of p45 v-abl kinase and K562 leukemia cells in vitro, II had IC50 of 0.78 and 4.82 .mu.M, resp.

L3 ANSWER 39 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:828284 HCAPLUS
DOCUMENT NUMBER: **123:227985**
TITLE: Arylidene and heteroarylidene oxindole derivatives as tyrosine kinase inhibitors
INVENTOR(S): Buzzetti, Franco; Longo, Antonio; Brasca, Maria Gabriella; Orzi, Fabrizio; Crugnola, Angelo; Ballinari, Dario; Mariani, Mariangela
PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.r.l., Italy
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9501349	A1	19950112	WO 1994-EP1715	19940526
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2142472	AA	19950112	CA 1994-2142472	19940526
AU 9469719	A1	19950124	AU 1994-69719	19940526
AU 679754	B2	19970710		
EP 658159	A1	19950621	EP 1994-918379	19940526
EP 658159	B1	20000823		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1111454	A	19951108	CN 1994-190452	19940526
JP 08500847	T2	19960130	JP 1994-503150	19940526
HU 72047	A2	19960328	HU 1995-954	19940526
EP 987263	A2	20000322	EP 1999-203366	19940526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE				
AT 195734	E	20000915	AT 1994-918379	19940526
ES 2152317	T3	20010201	ES 1994-918379	19940526
US 5656654	A	19970812	US 1994-263666	19940622
ZA 9404730	A	19950713	ZA 1994-4730	19940630
FI 9500859	A	19950224	FI 1995-859	19950224

PRIORITY APPLN. INFO.: GB 1993-13638 A 19930701
EP 1994-918379 A3 19940526
WO 1994-EP1715 W 19940526

OTHER SOURCE(S): MARPAT 123:227985
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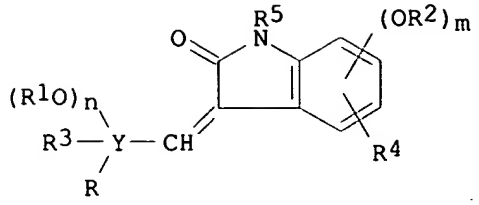

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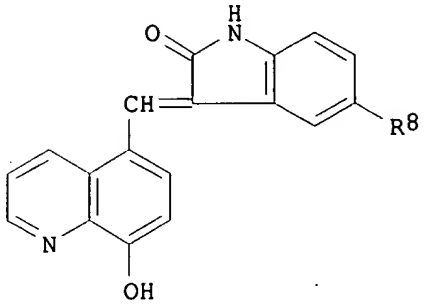


II

AB Title derivs. I [Y = naphthalene, tetralin, quinoline or isoquinoline system; R = H, plus oxo when Y is tetralin; R1, R2 independently = H, C1-6 alkyl or C2-6 alkanoyl; m = 0-2; n = 0-3; R3 independently = H, halo, cyano, C1-6 alkyl, carboxy, nitro or NR6R7 where R6, R7 independently = H, C1-6 alkyl; R5 = H, C1-6 alkyl] and their pharmaceutically acceptable salts, which are useful as tyrosine kinase inhibitors, are claimed. The E- and Z-isomers of approx. 85 compds. are specifically claimed. Several synthetic examples are given. For example, condensation of 8-hydroxyquinoline-5-carboxaldehyde with 5-hydroxy-2-oxindole in EtOH in the presence of piperidine at 60-70.degree. gave 60% title compd. II (R8 = OH). Among test results for 10 selected I for inhibition of p45 v-abl kinase in vitro, and for inhibition of cultured K562 human leukemia cell growth, II (R8 = Br) had IC50 values of 2.6 and 0.62 .mu.M, resp.

L3 ANSWER 40 OF 40 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:813058 HCAPLUS
DOCUMENT NUMBER: **123:208831**
TITLE: Biologically active 3-substituted oxindole derivatives useful as anti-**angiogenic** agents
INVENTOR(S): Heath, William Francis Heat, Jr.; McDonald, John Hampton III; Brasca, Maria Gabriella; Orzi, Fabrizio; Crugnola, Angelo; Ballinari, Dario; Mariani, Mariangela
PATENT ASSIGNEE(S): Pharmacia S.P.A., Italy
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9517181	A1	19950629	WO 1994-EP3664	19941108

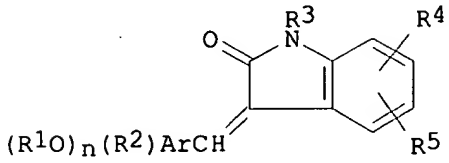
W: AU, BY, CA, HU, JP, KR, KZ, NO, PL, RU, UA
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

CA 2155098	AA	19950629	CA 1994-2155098	19941108
AU 9480612	A1	19950710	AU 1994-80612	19941108
AU 676958	B2	19970327		
EP 684820	A1	19951206	EP 1994-931583	19941108
EP 684820	B1	20010816		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
HU 73176	A2	19960628	HU 1995-2761	19941108
JP 08507089	T2	19960730	JP 1994-517121	19941108
AT 204168	E	20010915	AT 1994-931583	19941108
ES 2162871	T3	20020116	ES 1994-931583	19941108
ZA 9410204	A	19951110	ZA 1994-10204	19941212
US 5576330	A	19961119	US 1994-354215	19941212
IL 112010	A1	19981030	IL 1994-112010	19941216
NO 9503146	A	19950810	NO 1995-3146	19950810

PRIORITY APPLN. INFO.: GB 1993-26136 A 19931222
WO 1994-EP3664 W 19941108

OTHER SOURCE(S): MARPAT 123:208831

GI



I

AB Compds. I (Ar = naphthalene, tetralin, quinoline, isoquinoline, indole; n = 0 or an integer of 1 to 3; R1 = H, C1-6 alkyl, C2-6 alkanoyl; R2 = H, halogen, C1-6 alkyl, cyano, carboxy, nitro, NHR; R = H, C1-6 alkyl; R3 = H, C1-6 alkyl; R4 = H, OH, C1-6 alkoxy, C2-6 alkanoyloxy, carboxy, nitro, NHR; R5 = H, C1-6 alkyl, halogen) or a pharmaceutically acceptable salt thereof are useful as **angiogenesis** inhibitors. Products contg. an **angiogenesis** inhibitor or a pharmaceutically acceptable salt thereof and an antitumor agent are used as a combined prepn. for anticancer therapy. A compn. (for 10,000 tablets) contg. 3-[(3'-hydroxy-2'-tetralyl)methylen]-2-oxindole 250. lactose 800, corn starch 415, talc 30 and Mg stearate 5 g, resp., was formulated.

Compd (a) (date-limited)

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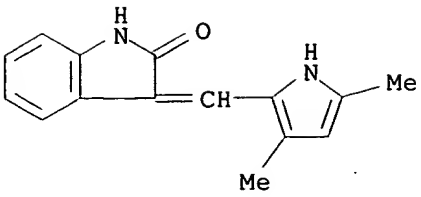
L6 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:640690 HCAPLUS
DOCUMENT NUMBER: 127:314804
TITLE: Assays for KDR/FLK-1 receptor tyrosine kinase inhibitors, and use of the inhibitors for treatment of vasculogenesis- and **angiogenesis**-related diseases
INVENTOR(S): Hirth, Klaus P.; McMahon, Gerald; Shawver, Laura K.
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9734920	A1	19970925	WO 1997-US3378	19970304 <--
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9720667	A1	19971010	AU 1997-20667	19970304 <--
PRIORITY APPLN. INFO.:			US 1996-621734	19960321 <--
			WO 1997-US3378	19970304 <--

AB Processes are disclosed for the identification of compds. and pharmaceutical compns. capable of selectively and potently inhibiting KDR/FLK-1 tyrosine kinase signal transduction in order to inhibit vasculogenesis and/or **angiogenesis**. The invention also relates to compds. and compns. identified using the methods of the invention and the use thereof for the treatment of disease relating to inappropriate vasculogenesis and/or **angiogenesis**. The invention provides an assay cascade comprised of several "filter steps" of increasing selectivity which identify a limited subset of candidate compds. affecting the **VEGF** receptor on the mol. level.

IT **204005-46-9**, SU 5416
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and **angiogenesis**-related diseases)

RN 204005-46-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



IT **204005-46-9**, SU 5416
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and **angiogenesis**-related diseases)

L6 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:140244 HCAPLUS
DOCUMENT NUMBER: 126:139901
TITLE: Indolinone compounds capable of modulating tyrosine kinase signal transduction
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9640116	A1	19961219	WO 1996-US8903	19960605	<--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
US 5880141	A	19990309	US 1995-485323	19950607	
CA 2192797	AA	19961219	CA 1996-2192797	19960605	<--
AU 9660441	A1	19961230	AU 1996-60441	19960605	<--
AU 706597	B2	19990617			
EP 769947	A1	19970502	EP 1996-918093	19960605	<--
EP 769947	B1	20010502			
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
BR 9606410	A	19971230	BR 1996-6410	19960605	<--
JP 10504323	T2	19980428	JP 1996-501363	19960605	<--
EP 934931	A2	19990811	EP 1999-103667	19960605	<--
EP 934931	A3	19991020			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI					
JP 2000026412	A2	20000125	JP 1999-159567	19960605	<--
AT 200863	E	20010515	AT 1996-918093	19960605	<--
ES 2159741	T3	20011016	ES 1996-918093	19960605	<--
JP 3231044	B2	20011119	JP 1997-501363	19960605	<--

NO 9605377	A	19970212	NO 1996-5377	19961213	<--
HK 1011933	A1	20020118	HK 1998-113193	19981211	<--
US 2002022626	A1	20020221	US 2000-617529	20000713	<--
US 2003108946	A1	20030612	US 2002-76621	20020219	<--

PRIORITY APPLN. INFO.:

US 1995-485323	A	19950607	<--
EP 1996-918093	A3	19960605	<--
JP 1997-501363	A3	19960605	<--
WO 1996-US8903	W	19960605	<--
US 1997-915366	A3	19970820	<--
US 2000-617529	B1	20000713	

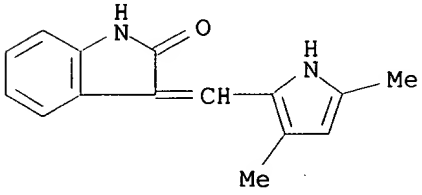
OTHER SOURCE(S): MARPAT 126:139901

AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

IT **204005-46-9P**, SU 5416
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indolinones capable of modulating tyrosine kinase signal transduction)

RN 204005-46-9 HCAPLUS

CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



IT **204005-46-9P**, SU 5416
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indolinones capable of modulating tyrosine kinase signal transduction)

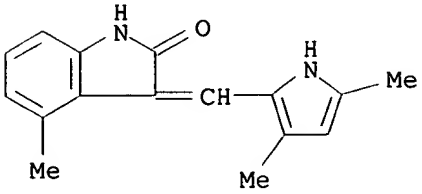
=> d ibib abs hitstr l10 1-3

L10 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:500184 HCAPLUS
DOCUMENT NUMBER: 133:234344
TITLE: DoMCoSAR: A Novel Approach for Establishing the Docking Mode That Is Consistent with the Structure-Activity Relationship. Application to HIV-1 Protease Inhibitors and VEGF Receptor Tyrosine Kinase Inhibitors
AUTHOR(S): Vieth, Michal; Cummins, David J.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 3020-3032
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB DoMCoSAR is a novel approach for statistically detg. the docking mode that is consistent with a structure-activity relationship. The approach establishes the binding mode for the compds. in a chem. series with the assumption that all mols. exhibit the same binding mode. It involves three stages. In the first stage all mols. that belong to a given chem. series are docked to the active site of the protein target. The only bias used in the docking at this stage involves the location of the protein binding site. Coordinates of the common substructure (CS) that results from the unbiased docking are then clustered to establish the major substructure docking modes. In the second stage all mols. are docked to the major docking modes (MDMs) with constraints based on the common substructure. The third stage generates, for the major docking modes, interaction-based descriptors that include electrostatic, VDW, strain, and solvation contributions. The problem of docking mode evaluation is now reduced to the question of which descriptor set is more predictive. To establish a quant. comparison of the descriptor sets assocd. with the major docking modes, we use 50 instances of random 4-fold cross-validation. For each 4-fold cross-validation the predictive squared correlation coeff. (R2) is computed. T-Tests are applied to establish significance of the differences in mean R for one docking mode vs. another. We test the methodol. on two test cases: HIV-1 protease inhibitors (Holloway et al. J. Med. Chem. 1995, 38, 305-317) and vascular endothelial growth factor (VEGF) receptor tyrosine kinase oxoindoles (Sun et al. J. Med. Chem. 1998, 41, 2588-2603). For both test cases there is statistically significant preference for the binding mode consistent with the x-ray structure. The appeal of this methodol. is that researchers gain the objectivity of statistical justification for the selected docking mode. The methodol. is relatively insensitive to subtle variations of the protein structure that include, but are not limited to, side chain and small backbone rearrangement during binding. In addn., predictive models that result from the approach can be used to further optimize chem. series.

IT **204005-54-9**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(VEGF kinase-inhibitor; DoMCoSAR - novel approach for establishing docking mode that is consistent with structure-activity relationship with application to HIV-1 protease inhibitors and VEGF receptor tyrosine kinase inhibitors)

RN 204005-54-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

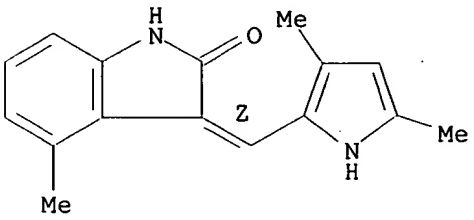
L10 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:429042 HCAPLUS
DOCUMENT NUMBER: 129:117426
TITLE: Synthesis and Biological Evaluations of 3-Substituted Indolin-2-ones: A Novel Class of Tyrosine Kinase Inhibitors That Exhibit Selectivity toward Particular Receptor Tyrosine Kinases
AUTHOR(S): Sun, Li; Tran, Ngoc; Tang, Flora; App, Harald; Hirth, Peter; McMahon, Gerald; Tang, Cho
CORPORATE SOURCE: SUGEN Inc, Redwood City, CA, 94063, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(14), 2588-2603
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 3-Substituted indolin-2-ones have been designed and synthesized as a novel class of tyrosine kinase inhibitors which exhibit selectivity toward different receptor tyrosine kinases (RTKs). These compds. have been evaluated for their relative inhibitory properties against a panel of RTKs in intact cells. By modifying the 3-substituted indolin-2-ones, we have identified compds. which showed selective inhibition of the ligand-dependent autophosphorylation of various RTKs at submicromolar levels in cells. Structure-activity anal. for these compds. and their relative potency and selectivity to inhibit particular RTKs has detd. that (1) 3-[(five-membered heteroaryl ring)methylidenyl]indolin-2-ones are highly specific against the VEGF (Flk-1) RTK activity, (2) 3-(substituted benzylidenyl)indolin-2-ones contg. bulky group(s) in the Ph ring at the C-3 position of indolin-2-ones showed high selectivity toward the EGF and Her-2 RTKs, and (3) the compd. contg. an extended side chain at the C-3 position of the indolin-2-one exhibited high potency and selectivity when tested against the PDGF and VEGF (Flk-1) RTKs. Recent published crystallog. data for two of these 3-substituted indolin-2-ones provides a rationale to suggest that these compds. may bind in the ATP binding pocket of RTKs. The structure-activity anal. supports the use of subsets of these compds. as specific chem. leads for the development of RTK-specific drugs with broad application for the treatment of human diseases.

IT **210303-58-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and evaluation of 3-substituted indolin-2-ones as inhibitors of selective growth factor receptors)

RN 210303-58-5 HCAPLUS
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-4-methyl-, (3Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:147306 HCAPLUS
DOCUMENT NUMBER: 128:204803
TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus Peter; Shawver, Laura Kay; et al.
PATENT ASSIGNEE(S): Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807695	A1	19980226	WO 1997-US14736	19970820
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CN 1155838	A	19970730	CN 1996-190616	19960605
EP 929520	A1	19990721	EP 1997-939480	19970820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6147106	A	20001114	US 1997-915366	19970820
JP 2001503736	T2	20010321	JP 1998-510973	19970820
EP 1247803	A2	20021009	EP 2002-77564	19970820
EP 1247803	A3	20021016		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 9741556	A1	19980306	AU 1997-41556	19970821
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.: US 1996-702232 A 19960823

US 1996-31585P	P	19961205
US 1996-31586P	P	19961205
US 1996-31588P	P	19961205
US 1996-32546P	P	19961205
US 1996-32547P	P	19961205
US 1997-45565P	P	19970505
US 1997-45566P	P	19970505
US 1997-45714P	P	19970505
US 1997-45715P	P	19970505
US 1997-46843P	P	19970505
US 1996-45715P	P	19961205
US 1997-31565P	P	19970505
EP 1997-939480	A3	19970820
US 1997-915366	A3	19970820
WO 1997-US14736	W	19970820
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 128:204803
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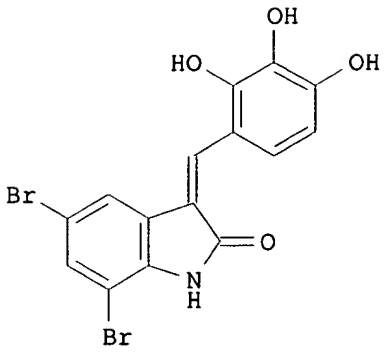


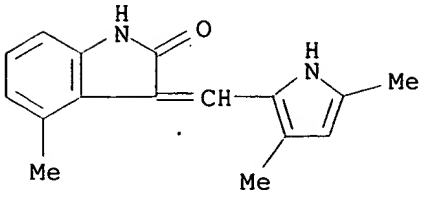
I

AB The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. The compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chem. substituents to the 3-[(indole-3-yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepd. by combinatorial condensation of certain (un)substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro.

IT **204005-54-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and testing of indolinone combinatorial library as protein kinase inhibitors)

RN 204005-54-9 HCAPLUS

CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr l8 1-8

L8 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:492716 HCAPLUS
DOCUMENT NUMBER: 139:63316
TITLE: Methods using a combination of a 3-heteroaryl-2-indolinone and a cyclooxygenase-2 inhibitor for the treatment of neoplasia
INVENTOR(S): Masferrer, Jaime L.; Cherrington, Julie M.; Leahy, Kathleen M.; Zweifel, Ben S.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 66 pp., Cont.-in-part of Appl. No. PCT/US99/30693.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003119895	A1	20030626	US 2002-150546	20020516
WO 2000038730	A2	20000706	WO 1999-US30693	19991222
WO 2000038730	A3	20001102		

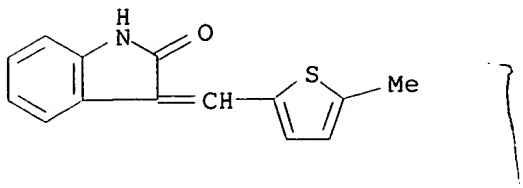
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-113786P P 19981223
WO 1999-US30693 A2 19991222
OTHER SOURCE(S): MARPAT 139:63316

AB The invention provides methods and compns. useful for treatment or prevention of neoplasia by administering a combination comprising a 3-heteroaryl-2-indolinone compd. (prepn. included) and a COX-2 selective inhibitor. Further provided are compns., pharmaceutical compns., and kits for treatment and prevention of neoplasia.

IT **186610-97-9P**, SU 5424
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heteroaryl indolinone-cyclooxygenase 2 inhibitor combination for treatment of neoplasia)

RN 186610-97-9 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)

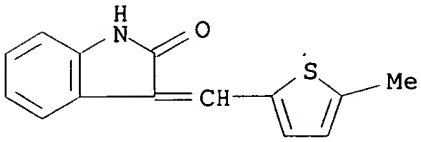


RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heteroaryl indolinone-cyclooxygenase 2 inhibitor combination for treatment of neoplasia

L8 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:107858 HCAPLUS
DOCUMENT NUMBER: 136:147463
TITLE: High-throughput preformulation of potential indolinone drug candidates
INVENTOR(S): Shenoy, Narmada
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 10 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002015938	A1	20020207	US 1998-182700	19981029

PRIORITY APPLN. INFO.: US 1997-63951P P 19971031
OTHER SOURCE(S): MARPAT 136:147463
AB The invention relates to a method of simultaneous high-throughput preformulation quantification of potential drug candidates, where an aliquot of a mixt. of solns. contg. different compds. is injected into a high pressure liq. chromatograph. The concn. of each compd. can be detd. by high pressure liq. chromatog. anal., and correlated to a physico-chem. property of the compd.
IT **186610-97-9**
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(high-throughput preformulation of potential drug candidates)
RN 186610-97-9 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:205317 HCAPLUS
DOCUMENT NUMBER: 130:252240
TITLE: Preparation of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 40 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

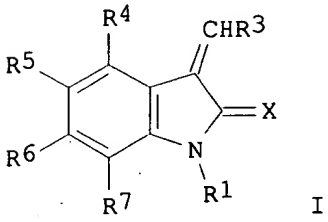
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5886020	A	19990323	US 1996-655226	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219
US 2003069421	A1	20030410	US 2002-201593	20020724

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A2	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-75271	B1	19980508
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 130:252240

GI



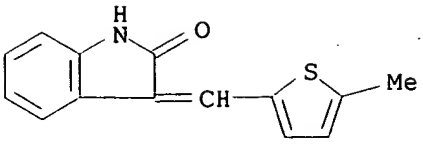
I

AB Title compds. [I; R1 = H or alkyl; R3 = ZR2; R2 = OR, NRaRb, 5-membered heteroaryl, etc.; R = H, alkyl, aryl; Ra,Rb = H, alkyl, COR; NRaRb = heterocyclyl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S; Z = (un)substituted 1,4-phenylene] were prepd. Thus, 2-oxindole was condensed with PhCHO to give 3-benzylidene-2-indolinone. Data for biol. activity of I were given.

IT **186610-97-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

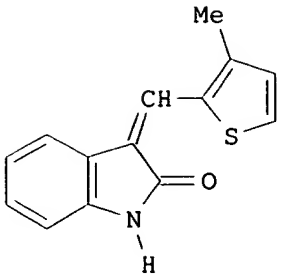
L8 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:193848 HCAPLUS
DOCUMENT NUMBER: 130:237471
TITLE: 3-(2-Alkoxybenzylidene)-2-indolinones and their analogs for the treatment of disease
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5883116	A	19990316	US 1996-655224	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A2	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 130:237471
GI



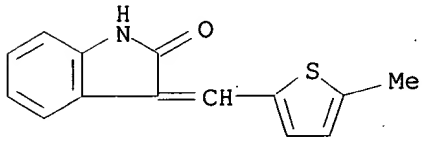
I

AB Indolinones such as I were prepd. for modulating tyrosine kinase signal transduction in order to regulate, modulate, and/or inhibit abnormal cell proliferation. Thus, a mixt. of 134.0 mg oxindole, 151.4 mg 3-methyl-2-thiophenecarboxaldehyde, and 3 drops of piperidine in 2 mL EtOH was stirred at 90.degree. for 3 h to give a 65% yield of I. In an ELISA assay to measure the inhibition of protein tyrosine kinase activity on the FLK-1 receptor, I showed an IC50 of 4.5 .mu.M.

IT **186610-97-9P**, SU 5424
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(3-(2-alkoxybenzylidene)-2-indolinones and their analogs for modulating tyrosine kinase signal transduction)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:193846 HCAPLUS

DOCUMENT NUMBER: 130:237470

TITLE: Preparation of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators

INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald

PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 485,233.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5883113	A	19990316	US 1996-659191	19960605
US 5880141	A	19990309	US 1995-485323	19950607

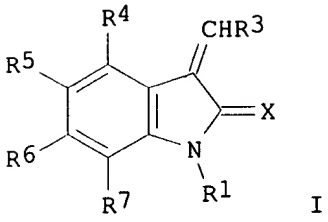
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 6225335	B1	20010501	US 1998-212494	19981215
US 6316635	B1	20011113	US 1999-293518	19990415
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A1	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 130:237470

GI



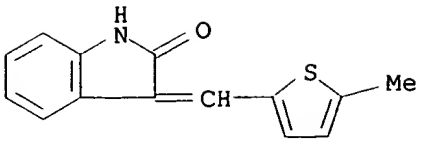
I

AB Title compds. [I; R1 = H or alkyl; R3 = ZR2, 5-membered heteroaryl, etc.; R2 = OR, NRaRb, etc.; R = H, alkyl, aryl, etc.; Ra,Rb = H, alkyl, COR, etc.; NRaRb = heterocyclyl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S; Z = (un)substituted 1,4-phenylene] were prepd. Thus, PhCHO was condensed with 2-oxindole to give I (R1 = R4-R7 = H, R3 = Ph, X = O). Data for biol. activity of I were given.

IT **186610-97-9P**, SU 5424
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



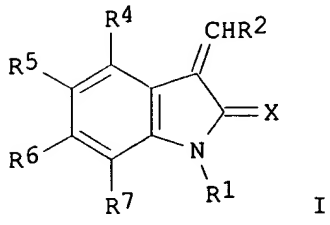
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:735056 HCAPLUS
DOCUMENT NUMBER: 129:330650
TITLE: Preparation of 3-benzylidene-2-indolinones and analogs as tyrosine kinase signal transduction modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen Inc., USA
SOURCE: U.S., 34 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5834504	A	19981110	US 1996-655225	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:
US 1995-485323 A2 19950607
EP 1996-918093 A3 19960605
JP 1997-501363 A3 19960605
US 1997-915366 A3 19970820
US 2000-617529 B1 20000713

OTHER SOURCE(S): MARPAT 129:330650
GI



I

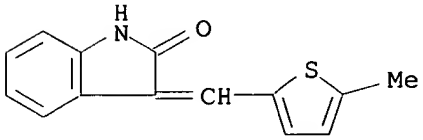
AB Title compds. [I; R1 = H or alkyl; R2 = 2-halo-4-hydroxy- or -alkoxyphenyl, 4-hydroxy- or -alkoxyphenyl, 4-(di)(alkyl)aminophenyl,

heteroaryl, etc.; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S] were prepd. Thus, oxindole was condensed with 2-chloro-4-methoxybenzaldehyde to give I (R1 = R4-R7 = H, R2 = 2-chloro-4-methoxyphenyl, X = O). Data for biol. activity of I were given.

IT **186610-97-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones and analogs as tyrosine kinase signal transduction modulators)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 181 THERE ARE 181 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

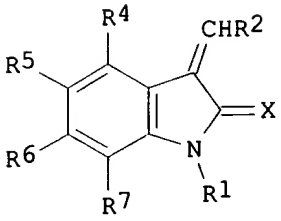
L8 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:542764 HCAPLUS
DOCUMENT NUMBER: 129:175549
TITLE: Preparation of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 37 pp., Cont.-in-part of U. S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5792783	A	19980811	US 1996-655223	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 6316635	B1	20011113	US 1999-293518	19990415
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:
US 1995-485323 A2 19950607
EP 1996-918093 A3 19960605
JP 1997-501363 A3 19960605
US 1996-655223 A2 19960605

US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A1	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 129:175549
GI



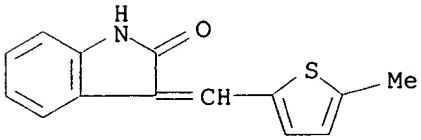
I

AB Title compds. [I; R1 = H or alkyl; R2 = (un)substituted (hetero)aryl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S] were prepd. Thus, oxindole was condensed with 4-pyridinecarboxaldehyde to give I (R1,R4-R7 = H, R2 = 4-pyridinyl, X = O). Data for biol. activity of I were given.

IT **186610-97-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:140244 HCAPLUS
DOCUMENT NUMBER: 126:139901
TITLE: Indolinone compounds capable of modulating tyrosine kinase signal transduction
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 133 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640116	A1	19961219	WO 1996-US8903	19960605
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
AU 9660441	A1	19961230	AU 1996-60441	19960605
AU 706597	B2	19990617		
EP 769947	A1	19970502	EP 1996-918093	19960605
EP 769947	B1	20010502		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9606410	A	19971230	BR 1996-6410	19960605
JP 10504323	T2	19980428	JP 1996-501363	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
AT 200863	E	20010515	AT 1996-918093	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
NO 9605377	A	19970212	NO 1996-5377	19961213
HK 1011933	A1	20020118	HK 1998-113193	19981211
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
WO 1996-US8903	W	19960605
US 1997-915366	A3	19970820
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 126:139901

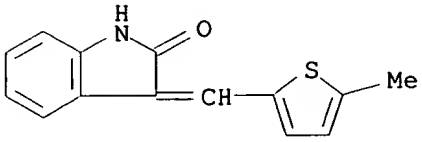
AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

IT **186610-97-9P**, SU 5424
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indolinones capable of modulating tyrosine kinase signal

transduction)

RN 186610-97-9 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



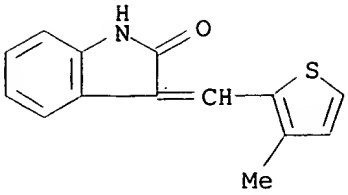
=> d ibib abs hitstr l12 1-8

L12 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:492716 HCAPLUS
DOCUMENT NUMBER: 139:63316
TITLE: Methods using a combination of a 3-heteroaryl-2-indolinone and a cyclooxygenase-2 inhibitor for the treatment of neoplasia
INVENTOR(S): Masferrer, Jaime L.; Cherrington, Julie M.; Leahy, Kathleen M.; Zweifel, Ben S.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 66 pp., Cont.-in-part of Appl. No. PCT/US99/30693.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003119895	A1	20030626	US 2002-150546	20020516
WO 2000038730	A2	20000706	WO 1999-US30693	19991222
WO 2000038730	A3	20001102		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-113786P P 19981223
WO 1999-US30693 A2 19991222
OTHER SOURCE(S): MARPAT 139:63316
AB The invention provides methods and compns. useful for treatment or prevention of neoplasia by administering a combination comprising a 3-heteroaryl-2-indolinone compd. (prepn. included) and a COX-2 selective inhibitor. Further provided are compns., pharmaceutical compns., and kits for treatment and prevention of neoplasia.
IT **186610-98-0P**, SU 5427
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heteroaryl indolinone-cyclooxygenase 2 inhibitor combination for treatment of neoplasia)
RN 186610-98-0 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)

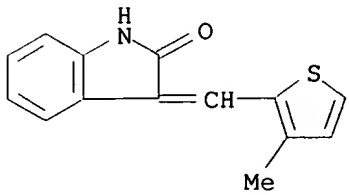


RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heteroaryl indolinone-cyclooxygenase 2 inhibitor combination for treatment of neoplasia

L12 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:107858 HCAPLUS
DOCUMENT NUMBER: 136:147463
TITLE: High-throughput preformulation of potential indolinone drug candidates
INVENTOR(S): Shenoy, Narmada
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 10 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002015938	A1	20020207	US 1998-182700	19981029
PRIORITY APPLN. INFO.:			US 1997-63951P P	19971031

OTHER SOURCE(S): MARPAT 136:147463
AB The invention relates to a method of simultaneous high-throughput preformulation quantification of potential drug candidates, where an aliquot of a mixt. of solns. contg. different compds. is injected into a high pressure liq. chromatograph. The concn. of each compd. can be detd. by high pressure liq. chromatog. anal., and correlated to a physico-chem. property of the compd.
IT **186610-98-0**
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(high-throughput preformulation of potential drug candidates)
RN 186610-98-0 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



L12 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:205317 HCAPLUS

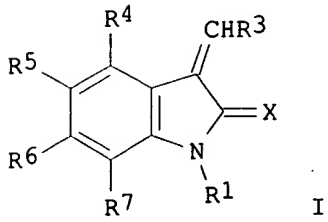
DOCUMENT NUMBER: 130:252240
TITLE: Preparation of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 40 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5886020	A	19990323	US 1996-655226	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219
US 2003069421	A1	20030410	US 2002-201593	20020724

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A2	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-75271	B1	19980508
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 130:252240
GI

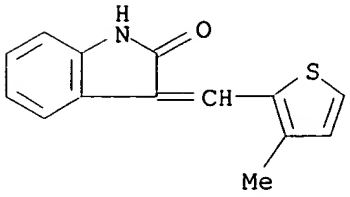


I

AB Title compds. [I; R1 = H or alkyl; R3 = ZR2; R2 = OR, NRaRb, 5-membered heteroaryl, etc.; R = H, alkyl, aryl; Ra,Rb = H, alkyl, COR; NRaRb = heterocyclyl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S; Z =

(un)substituted 1,4-phenylene] were prepd. Thus, 2-oxindole was condensed with PhCHO to give 3-benzylidene-2-indolinone. Data for biol. activity of I were given.

IT **186610-98-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators)
RN 186610-98-0 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

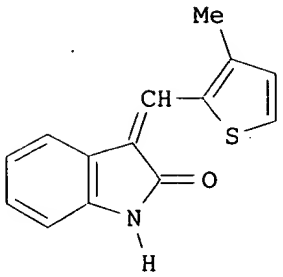
L12 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:193848 HCAPLUS
DOCUMENT NUMBER: 130:237471
TITLE: 3-(2-Alkoxybenzylidene)-2-indolinones and their analogs for the treatment of disease
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5883116	A	19990316	US 1996-655224	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:
US 1995-485323 A2 19950607
EP 1996-918093 A3 19960605
JP 1997-501363 A3 19960605
US 1996-655223 A2 19960605
US 1996-655224 A2 19960605

US 1996-655226 A2 19960605
US 1996-655255 B2 19960605
US 1996-659191 A2 19960605
US 1996-702232 B1 19960823
US 1997-915366 A3 19970820
US 2000-617529 B1 20000713

OTHER SOURCE(S): MARPAT 130:237471
GI



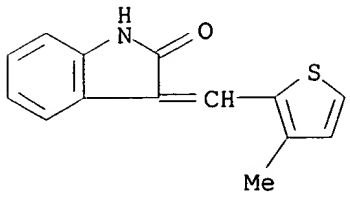
I

AB Indolinones such as I were prepd. for modulating tyrosine kinase signal transduction in order to regulate, modulate, and/or inhibit abnormal cell proliferation. Thus, a mixt. of 134.0 mg oxindole, 151.4 mg 3-methyl-2-thiophenecarboxaldehyde, and 3 drops of piperidine in 2 mL EtOH was stirred at 90.degree. for 3 h to give a 65% yield of I. In an ELISA assay to measure the inhibition of protein tyrosine kinase activity on the FLK-1 receptor, I showed an IC50 of 4.5 .mu.M.

IT **186610-98-0P**, SU 5427
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(3-(2-alkoxybenzylidene)-2-indolinones and their analogs for modulating tyrosine kinase signal transduction)

RN 186610-98-0 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:193846 HCAPLUS
DOCUMENT NUMBER: 130:237470
TITLE: Preparation of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators

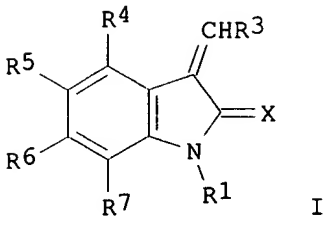
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 485,233.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5883113	A	19990316	US 1996-659191	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 6225335	B1	20010501	US 1998-212494	19981215
US 6316635	B1	20011113	US 1999-293518	19990415
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A1	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 130:237470
GI



I

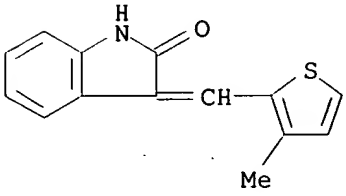
AB Title compds. [I; R1 = H or alkyl; R3 = ZR2, 5-membered heteroaryl, etc.; R2 = OR, NRaRb, etc.; R = H, alkyl, aryl, etc.; Ra,Rb = H, alkyl, COR, etc.; NRaRb = heterocyclyl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S; Z = (un)substituted 1,4-phenylene] were prepd. Thus, PhCHO was

condensed with 2-oxindole to give I (R1 = R4-R7 = H, R3 = Ph, X = O). Data for biol. activity of I were given.

IT **186610-98-0P**, SU 5427
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones as tyrosine kinase activity modulators)

RN 186610-98-0 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



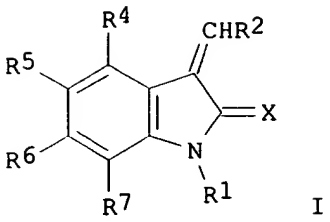
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:735056 HCAPLUS
DOCUMENT NUMBER: 129:330650
TITLE: Preparation of 3-benzylidene-2-indolinones and analogs as tyrosine kinase signal transduction modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen Inc., USA
SOURCE: U.S., 34 pp., Cont.-in-part of U.S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5834504	A	19981110	US 1996-655225	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:
US 1995-485323 A2 19950607
EP 1996-918093 A3 19960605
JP 1997-501363 A3 19960605
US 1997-915366 A3 19970820
US 2000-617529 B1 20000713

OTHER SOURCE(S): MARPAT 129:330650
GI



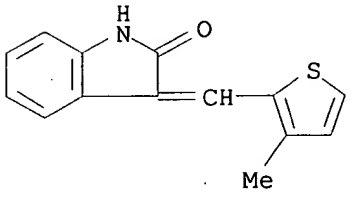
I

AB Title compds. [I; R1 = H or alkyl; R2 = 2-halo-4-hydroxy- or -alkoxyphenyl, 4-hydroxy- or -alkoxyphenyl, 4-(di)(alkyl)aminophenyl, heteroaryl, etc.; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S] were prepd. Thus, oxindole was condensed with 2-chloro-4-methoxybenzaldehyde to give I (R1 = R4-R7 = H, R2 = 2-chloro-4-methoxyphenyl, X = O). Data for biol. activity of I were given.

IT **186610-98-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-benzylidene-2-indolinones and analogs as tyrosine kinase signal transduction modulators)

RN 186610-98-0 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 181 THERE ARE 181 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:542764 HCAPLUS
DOCUMENT NUMBER: 129:175549
TITLE: Preparation of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 37 pp., Cont.-in-part of U. S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5792783	A	19980811	US 1996-655223	19960605

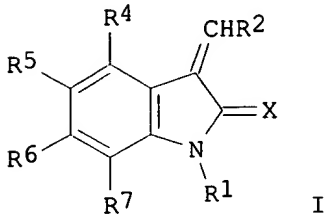
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 6316635	B1	20011113	US 1999-293518	19990415
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A1	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 129:175549

GI



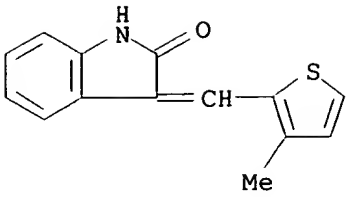
I

AB Title compds. [I; R1 = H or alkyl; R2 = (un)substituted (hetero)aryl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S] were prepd. Thus, oxindole was condensed with 4-pyridinecarboxaldehyde to give I (R1,R4-R7 = H, R2 = 4-pyridinyl, X = O). Data for biol. activity of I were given.

IT **186610-98-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators)

RN 186610-98-0 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:140244 HCAPLUS
DOCUMENT NUMBER: 126:139901
TITLE: Indolinone compounds capable of modulating tyrosine kinase signal transduction
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640116	A1	19961219	WO 1996-US8903	19960605
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
AU 9660441	A1	19961230	AU 1996-60441	19960605
AU 706597	B2	19990617		
EP 769947	A1	19970502	EP 1996-918093	19960605
EP 769947	B1	20010502		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9606410	A	19971230	BR 1996-6410	19960605
JP 10504323	T2	19980428	JP 1996-501363	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
AT 200863	E	20010515	AT 1996-918093	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
NO 9605377	A	19970212	NO 1996-5377	19961213
HK 1011933	A1	20020118	HK 1998-113193	19981211
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US	1995-485323	A 19950607
EP	1996-918093	A3 19960605
JP	1997-501363	A3 19960605
WO	1996-US8903	W 19960605
US	1997-915366	A3 19970820
US	2000-617529	B1 20000713

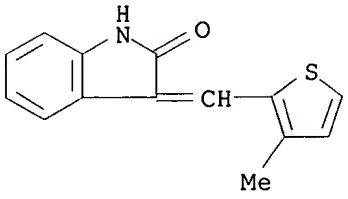
OTHER SOURCE(S): MARPAT 126:139901

AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

IT **186610-98-0P**, SU 5427
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indolinones capable of modulating tyrosine kinase signal transduction)

RN 186610-98-0 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



=> d ibib abs hitstr l14 1-13

L14 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:532550 HCAPLUS
DOCUMENT NUMBER: 139:95434
TITLE: Chorioallantoic membrane (CAM) assay for identifying agents with biological effects
INVENTOR(S): Hazel, Susan Jane
PATENT ASSIGNEE(S): Medvet Science Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055530	A1	20030710	WO 2002-AU1759	20021220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-343345P P 20011221
AU 2002-2002950565A 20020802
AU 2002-2002952008A 20021011

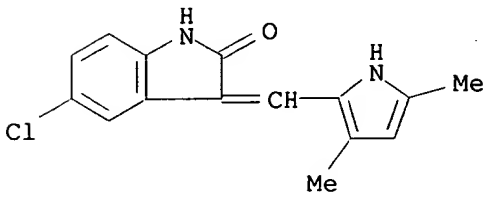
AB The invention discloses assays and, particularly, chorioallantoic membrane (CAM) assays for identifying and/or assessing agents with biol. effects (e.g. agents which effect angiogenesis, or promote neurogenesis, or which are capable of silencing particular gene(s)), and for assessing toxicity of various agents (e.g. for toxicity testing of candidate agents with desirable biol. effects). The CAM assay comprises (i) sep. placing 2-4 day old embryos from chicken or the like, which have been removed from their shells, into sep. cup means to support the embryos through steps (ii)-(vii), wherein each cup means also contains a suitable amt. of a growth medium; (ii) incubating the embryos for about 24 h; (iii) measuring the size of the CAM developed from each embryo, and grouping the embryos having CAMs of substantially similar size; (iv) applying to one or more embryo(s) within a selected group, a candidate agent, wherein the candidate agent is applied to the/each embryo by absorbing the candidate agent onto a porous or otherwise sorbent support and placing the support into contact with the CAM such that at least a portion of the candidate agent thereafter diffuses from the support to the CAM; (v) incubating the embryo(s) of step (iv) and a control embryo(s) from the same selected group for about 18-24 h; (vi) administering to the CAM of each embryo of step (v) a contrasting compn. comprising skim milk or the like and a suitably colored dyestuff; and (vii) detg. whether the candidate agent affects the CAM and/or embryo by observing differences between the CAM(s) and/or embryo(s) to which the candidate agent was applied and the CAM(s) and/or embryo(s) of the control embryo(s) of the same selected group.

IT **186611-56-3**, SU5614
RL: PAC (Pharmacological activity); BIOL (Biological study)

(chorioallantoic membrane assay for identifying agents with biol. effects)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:492716 HCAPLUS

DOCUMENT NUMBER: 139:63316

TITLE: Methods using a combination of a 3-heteroaryl-2-indolinone and a cyclooxygenase-2 inhibitor for the treatment of neoplasia

INVENTOR(S): Masferrer, Jaime L.; Cherrington, Julie M.; Leahy, Kathleen M.; Zweifel, Ben S.

PATENT ASSIGNEE(S): Pharmacia Corporation, USA

SOURCE: U.S. Pat. Appl. Publ., 66 pp., Cont.-in-part of Appl. No. PCT/US99/30693.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 12

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003119895	A1	20030626	US 2002-150546	20020516
WO 2000038730	A2	20000706	WO 1999-US30693	19991222
WO 2000038730	A3	20001102		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

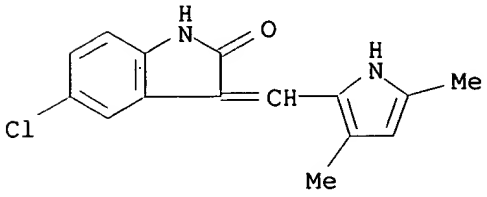
PRIORITY APPLN. INFO.: US 1998-113786P P 19981223
WO 1999-US30693 A2 19991222

OTHER SOURCE(S): MARPAT 139:63316

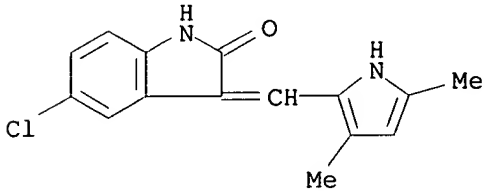
AB The invention provides methods and compns. useful for treatment or prevention of neoplasia by administering a combination comprising a 3-heteroaryl-2-indolinone compd. (prepn. included) and a COX-2 selective inhibitor. Further provided are compns., pharmaceutical compns., and kits for treatment and prevention of neoplasia.

IT **186611-56-3 186611-56-3D**, prodrug derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(heteroaryl indolinone-cyclooxygenase 2 inhibitor combination for treatment of neoplasia)
RN 186611-56-3 HCAPLUS
CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 186611-56-3 HCAPLUS
CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



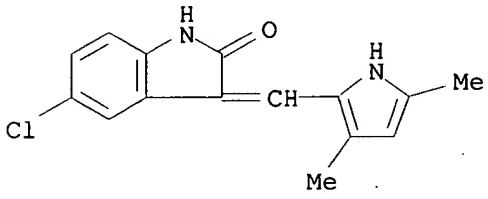
L14 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:122396 HCAPLUS
DOCUMENT NUMBER: 139:62799
TITLE: The protein tyrosine kinase inhibitor SU5614 inhibits FLT3 and induces growth arrest and apoptosis in AML-derived cell lines expressing a constitutively activated FLT3
AUTHOR(S): Spiekermann, Karsten; Dirschinger, Ralf J.; Schwab, Ruth; Bagrintseva, Ksenia; Faber, Florian; Buske, Christian; Schnittger, Susanne; Kelly, Louise M.; Gilliland, D. Gary; Hiddemann, Wolfgang
CORPORATE SOURCE: Department of Medicine III, Clinical Cooperative Group "Leukemia," GSF National Research Center for Environment and Health, University Hospital Grosshadern, Munich, 81377, Germany
SOURCE: Blood (2003), 101(4), 1494-1504
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activating mutations of the protein tyrosine kinase (PTK) FLT3 can be found in approx. 30% of patients with acute myeloid leukemia (AML), thereby representing the most frequent single genetic alteration in AML. These mutations occur in the juxtamembrane (FLT3 length mutations; FLT3-LMs) and the second tyrosine kinase domain of FLT3-TKD and confer interleukin 3 (IL-3)-independent growth to Ba/F3 cells. In the mouse bone marrow transplantation model, FLT3-LMs induce a myeloproliferative syndrome stressing their transforming activity in vivo. In this study, we

analyzed the pro-proliferative and antiapoptotic potential of FLT3 in FLT3-LM/TKD-mutation-transformed Ba/F3 cells and AML-derived cell lines. The PTK inhibitor SU5614 has inhibitory activity for FLT3 and selectively induces growth arrest, apoptosis, and cell cycle arrest in Ba/F3 and AML cell lines expressing a constitutively activated FLT3. In addn., the compd. reverts the anti-apoptotic and pro-proliferative activity of FLT3 ligand (FL) in FL-dependent cells. No cytotoxic activity of SU5614 was found in leukemic cell lines that express a nonactivated FLT3 or no FLT3 protein. At the biochem. level, SU5614 down-regulated the activity of the hyperphosphorylated FLT3 receptor and its down-stream targets, signal transducer and activator of (STAT) 3, STAT5, and mitogen-activated protein kinase (MAPK), and the STAT5 target genes BCL-XL and p21. Our results show that SU5614 is a PTK inhibitor of FLT3 and has antiproliferative and proapoptotic activity in AML-derived cell lines that endogenously express an activated FLT3 receptor. The selective and potent cytotoxicity of FLT3 PTK inhibitors support a clin. strategy of targeting FLT3 as a new mol. treatment option for patients with FLT3-LM/TKD-mutation+ AML.

IT **186611-56-3**, SU5614
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein tyrosine kinase inhibitor SU5614 inhibits FLT3 and induces growth arrest and apoptosis in AML-derived cell lines expressing constitutively activated FLT3)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:805255 HCAPLUS

DOCUMENT NUMBER: 138:314076

TITLE: SU5416 and SU5614 inhibit kinase activity of wild-type and mutant FLT3 receptor tyrosine kinase

AUTHOR(S): Yee, Kevin W. H.; O'Farrell, Anne Marie; Smolich, Beverly D.; Cherrington, Julie M.; McMahon, Gerald; Wait, Cecily L.; McGreevey, Laura S.; Griffith, Diana J.; Heinrich, Michael C.

CORPORATE SOURCE: Department of Medicine, Division of Hematology and Medical Oncology, Portland Veterans Affairs Medical Center, Oregon Health and Science University, Portland, USA

SOURCE: Blood (2002), 100(8), 2941-2949
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

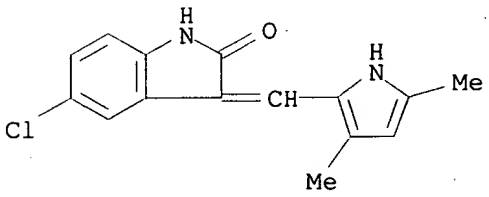
AB Internal tandem duplication (ITd) in the juxtamembrane portion of Fms-like tyrosine kinase 3 (FLT3), a type III receptor tyrosine kinase (RTK), is

the most common mol. defect assocd. with acute myeloid leukemia (AML). The high prevalence of this activating mutation makes it a potential target for molecularly based therapy. Indolinone tyrosine kinase inhibitors have known activity against KIT, another member of the type III RTK family. Given the conserved homol. between members of this family, we postulated that the activity of some KIT inhibitors would extend to FLT3. We used various leukemic cell lines (BaF3, MV 4-11, RS 4;11) to test the activity of indolinone compds. against the FLT3 kinase activity of both wild-type (WT) and ITD isoforms. Both SU5416 and SU5614 were capable of inhibiting autophosphorylation of ITD and WT FLT3 (SU5416 concn. that inhibits 50% [IC50], 100 nM; and SU5614 IC50 10 nM). FLT3-dependent activation of the downstream signaling proteins mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 5 (STAT5) was also inhibited by treatment in the same concn. rages. FLT3 inhibition by SU5416 and SU5614 resulted in reduced proliferation (IC50, 250 nM and 100 nM, resp.) and induction of apoptosis of FLT3 ITD-pos. leukemic cell lines. Treatment of these cells with an alternative growth factor (granulocyte-macrophage colony-stimulating factor [GM-CSF]) restored MAPK signaling and cellular proliferation, demonstrating specificity of the obsd. inhibitory effects. We conclude that SU5416 and SU5614 are potent inhibitors of FLT3. Our finding that inhibition of FLT3 induces apoptosis of leukemic cells supports the feasibility of targeting FLT3 as a novel treatment strategy for AML.

IT **186611-56-3**, SU5614
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SU5416 and SU5614 inhibit activity of FLT3 receptor tyrosine kinase and induce apoptosis of leukemic cells)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:628660 HCAPLUS
DOCUMENT NUMBER: 137:346843
TITLE: Effects of vascular endothelial and platelet-derived growth factor receptor inhibitors on long-term cultures from normal human bone marrow
AUTHOR(S): Duhrsen, Ulrich; Martinez, Tanja; Vohwinkel, Gabi; Ergun, Suleyman; Sun, Li; McMahon, Gerald; Durig, Jan; Hossfeld, Dieter Kurt; Fiedler, Walter
CORPORATE SOURCE: Zentrum fur Innere Medizin, Abteilung fur Hamatologie, Universitatsklinikum Essen, Germany
SOURCE: Growth Factors (2001), 19(1), 1-17
CODEN: GRFAEC; ISSN: 0897-7194
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal

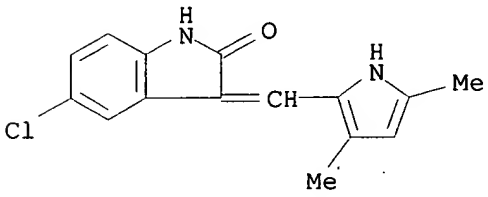
LANGUAGE: English

AB Endothelial cells and fibroblasts are important constituents of the hemopoietic microenvironment. Growth and function of these cells are controlled by a variety of cytokines, including VEGF and PDGF. The authors analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compds. SU5614 and SU5768) on the performance of long-term cultures from normal human bone marrow. In developing cultures, the inhibitors induced a dose-dependent redn. in stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell prodn. and an increase in fat cells. For SU5614, the concn. inhibiting stroma formation by 50% (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the resp. values were 871 nM and 331 nM. Changes in stroma compn. and inhibition of hemopoietic cell prodn. were also demonstrable after delayed addn. of the inhibitors to established cultures. By contrast, hemopoietic colony formation in clonogenic agar cultures was unimpaired (IC50 not reached at 100 .mu.M). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was assocd. with decreased levels in conditioned media of granulocyte-macrophage colony-stimulating factor, interleukin-6 and leptin. VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have therapeutic potential in stroma diseases such as myelofibrosis. Since they weaken the stimulatory signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases.

IT **186611-56-3**, SU5614
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PDGF and VEGF inhibitors biochem. and cellular characterization using bone marrow endothelial cells and fibroblasts)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:561903 HCAPLUS

DOCUMENT NUMBER: 138:163075

TITLE: The protein tyrosine kinase inhibitor SU5614 inhibits VEGF-induced endothelial cell sprouting and induces growth arrest and apoptosis by inhibition of c-kit in AML cells

AUTHOR(S): Spiekermann, Karsten; Faber, Florian; Voswinckel, Robert; Hiddemann, Wolfgang

CORPORATE SOURCE: Clinical Cooperative Group "Leukemia", University Hospital Grosshadern, Department of Medicine III, GSF

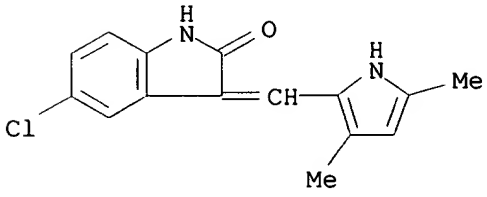
National Research Center for Environment and Health, Munich, Germany
SOURCE: Experimental Hematology (New York, NY, United States) (2002), 30(7), 767-773
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenesis, the process of new blood vessel formation, is a crit. process during growth and metastasis of solid tumors and might also represent a promising therapeutical target in patients with acute myeloid leukemia (AML). In this study, we analyzed the expression of vascular endothelial growth factor receptors (VEGFR)-1/2 and its ligand VEGF in AML cell lines and characterized the inhibitory activity of the protein tyrosine kinase (PTK) inhibitor SU5614 on human endothelial and leukemic cells. Intracellular VEGF expression was detected in 9 of 10 leukemic cell lines. In contrast, VEGFR-1 and VEGFR-2 expression was restricted to 6 and 2 out of 10 cell lines, resp. Although SU5614 was a potent inhibitor of the VEGF-induced endothelial cell sprouting in vitro, the sensitivity of leukemic cells toward the growth inhibitory activity of the compd. was detd. by the c-kit, but not by the VEGFR-1/2 expression. SU5614 induced growth arrest and apoptosis in c-kit-expressing Kasumi-1, UT-7, and M-07e cells and inhibited the stem cell factor (SCF)-induced tyrosine phosphorylation of c-kit. The sensitivity of Kasumi-1 cells towards the growth inhibitory activity of SU5614 was caused by an autocrine prodn. of SCF, but not by transforming mutations of c-kit. Our data provide strong evidence that SU5614 has a dual mode of action, and by direct inhibition of c-kit in AML cells and by inhibition of VEGFR-2 in endothelial cells, it might represent a novel treatment option for patients with c-kit+ AML.

IT **186611-56-3**, SU5614
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein tyrosine kinase inhibitor SU5614 inhibits VEGF-induced endothelial cell sprouting and induces growth arrest and apoptosis by inhibition of c-kit in AML cells)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:107858 HCAPLUS
DOCUMENT NUMBER: 136:147463
TITLE: High-throughput preformulation of potential indolinone drug candidates
INVENTOR(S): Shenoy, Narmada
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 10 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002015938	A1	20020207	US 1998-182700	19981029

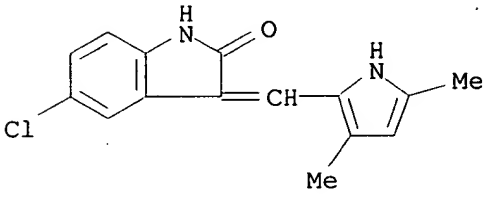
PRIORITY APPLN. INFO.: US 1997-63951P P 19971031
OTHER SOURCE(S): MARPAT 136:147463

AB The invention relates to a method of simultaneous high-throughput preformulation quantification of potential drug candidates, where an aliquot of a mixt. of solns. contg. different compds. is injected into a high pressure liq. chromatograph. The concn. of each compd. can be detd. by high pressure liq. chromatog. anal., and correlated to a physico-chem. property of the compd.

IT **186611-56-3**
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(high-throughput preformulation of potential drug candidates)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L14 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:472477 HCAPLUS
DOCUMENT NUMBER: 135:56059
TITLE: Methods of modulating c-kit tyrosine protein kinase function with indolinone compounds
INVENTOR(S): Lipson, Ken; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045689	A2	20010628	WO 2000-US35009	20001222
WO 2001045689	A3	20020103		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002010203 A1 20020124 US 2000-741842 20001222

EP 1255536 A2 20021113 EP 2000-991704 20001222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 1999-171693P P 19991222

WO 2000-US35009 W 20001222

OTHER SOURCE(S): MARPAT 135:56059

AB The invention concerns indolinone compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders such as cancers characterized by over-activity or inappropriate activity of c-kit kinase.

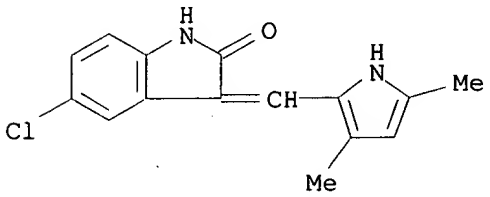
IT **186611-56-3**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(indolinone derivs. for c-kit tyrosine protein kinase function modulation)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L14 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:354377 HCAPLUS

DOCUMENT NUMBER: 135:146994

TITLE: Indolinone tyrosine kinase inhibitors block Kit activation and growth of small-cell lung cancer cells

AUTHOR(S): Krystal, Geoffrey W.; Honsawek, Sittisak; Kiewlich, David; Liang, Congxin; Vasile, Stefan; Sun, Li; McMahon, Gerald; Lipson, Kenneth E.

CORPORATE SOURCE: Departments of Internal Medicine and Microbiology/Immunology, McGuire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, 23249, USA

SOURCE: Cancer Research (2001), 61(9), 3660-3668

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

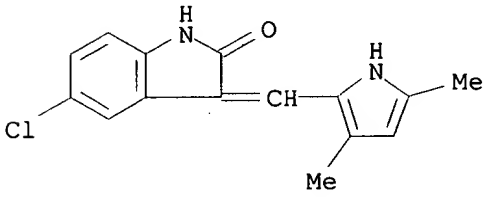
AB Six indolinone tyrosine kinase inhibitors were characterized for their ability to inhibit Kit kinase and for their effects on the growth of small-cell lung cancer (SCLC) cell lines. All six compds. were potent inhibitors of Kit kinase in a biochem. assay. A homol. model of compd. binding to the ATP-binding site could account for the increased potency caused by the addn. of a propionate moiety to the indolinone core but not that caused by addn. of a chloride moiety. Although all of the compds. tested were potent in the biochem. assay, several exhibited significantly

less potency in cellular kinase assays. Their effects on stem cell factor (SCF)-dependent Kit autophosphorylation and SCLC cell growth were also examd. Inhibition of SCF-stimulated Kit activation and cell growth of the H526 cell line was concn. dependent. At concns. that inhibited SCF-stimulated H526 cell growth, there was little effect on insulin-like growth factor-1-stimulated growth, suggesting that these compds. exhibit reasonable selectivity for inhibition of Kit-mediated proliferation. Higher concns. of the compds. were needed to inhibit serum-stimulated growth. Of the six compds. examd., SU5416 and SU6597 possessed the best cellular potency and, therefore, their effect on the growth of multiple SCLC cell lines in serum-contg. media was examd. In addn. to inhibiting proliferation, these compds. also induced cell death of several SCLC cell lines, but not of normal human diploid fibroblasts, in complete media. These observations suggest that Kit kinase inhibitors such as these may offer a new approach for inhibiting Kit-mediated proliferation of tumors such as SCLC, gastrointestinal stromal tumors, seminomas, and leukemias.

IT **186611-56-3**, SU 5614
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(indolinone-type tyrosine kinase inhibitors blockade of Kit activation and growth of small-cell lung cancer cells)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:431391 HCAPLUS
DOCUMENT NUMBER: 133:246860
TITLE: Indolinone derivatives inhibit constitutively activated KIT mutants and kill neoplastic mast cells
AUTHOR(S): Ma, Yongsheng; Carter, Eric; Wang, Xiaomei; Shu, Chang; McMahon, Gerald; Longley, B. Jack
CORPORATE SOURCE: Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
SOURCE: Journal of Investigative Dermatology (2000), 114(2), 392-394
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

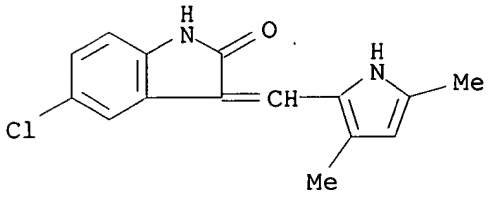
AB Mastocytosis is a neoplastic disease caused at least in part by somatic mutations of the c-KIT protooncogene resulting in constitutive activation of its protein product, KIT, the receptor tyrosine kinase for stem cell factor. KIT stimulates mast cell proliferation and prevents apoptosis of neoplastic mast cells. To develop potential therapies for mastocytosis we used indolinones, small mols. that inhibit tyrosine kinases. Four

indolinone derivs. (SU4984, SU6663, SU6577, and SU5614) inhibited wild-type KIT, but variably inhibited constitutively activated KIT mutants. SU4984, SU6577, and SU5614 were effective against KIT with juxtamembrane activating mutations, whereas only SU6577 could suppress KIT contg. either juxtamembrane or kinase domain activating mutations. Furthermore, SU4984, SU6577, and SU5614 killed neoplastic mast cells expressing a juxtamembrane-mutated KIT, whereas SU4984 and SU6577 killed neoplastic mast cells expressing KIT bearing a kinase domain mutation. These data show a direct correlation between inhibition of constitutively activated KIT and the death of neoplastic mast cells, and point to specific tyrosine kinase inhibitors as a potential therapy aimed directly at a cause of mastocytosis.

IT **186611-56-3**, SU 5614
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolinone derivs. inhibit activated KIT mutants and kill neoplastic mast cells)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:626172 HCAPLUS

DOCUMENT NUMBER: 131:257441

TITLE: Heterocyclic families of compounds [tricyclic-based indolinones and pyrazolecarboxylic acid amides] for the modulation of tyrosine protein kinase

INVENTOR(S): Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang, Congxin; McMahon, Gerald; Mohammadi, Moosa; Schlessinger, Joseph; Shawver, Laura K.; Sun, Li; Tang, Peng C.; Ullrich, Axel

PATENT ASSIGNEE(S): Sugen, Inc., USA; New York University; Max-Planck Institut fur Biochemie

SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948868	A2	19990930	WO 1999-US6468	19990326
WO 9948868	A3	20000224		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2325935	AA	19990930	CA 1999-2325935	19990326	
AU 9933635	A1	19991018	AU 1999-33635	19990326	
EP 1066257	A2	20010110	EP 1999-915018	19990326	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002507598	T2	20020312	JP 2000-537851	19990326	
US 6514981	B1	20030204	US 1999-283657	19990401	
US 2002022626	A1	20020221	US 2000-617529	20000713	
US 2003108946	A1	20030612	US 2002-76621	20020219	

PRIORITY APPLN. INFO.:

US 1998-79713P	P	19980326
US 1998-80422P	P	19980402
US 1998-81792P	P	19980415
US 1998-82056P	P	19980416
US 1998-89397P	P	19980615
US 1998-89521P	P	19980616
US 1998-98783P	P	19980901
US 1997-915366	A3	19970820
WO 1999-US6468	W	19990326
US 2000-617529	B1	20000713

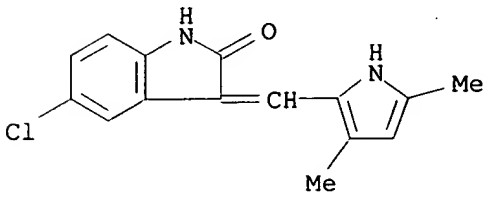
OTHER SOURCE(S): MARPAT 131:257441
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

IT **186611-56-3P**, 5-Chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydroindol-2-one
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of pyrazolecarboxylic acid amides and

(arylmethylene)indolinones as protein tyrosine kinase modulators)
RN 186611-56-3 HCAPLUS
CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L14 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:542764 HCAPLUS
DOCUMENT NUMBER: 129:175549
TITLE: Preparation of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 37 pp., Cont.-in-part of U. S. Ser. No. 485,323.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

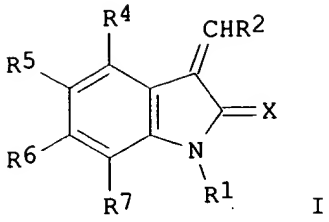
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5792783	A	19980811	US 1996-655223	19960605
US 5880141	A	19990309	US 1995-485323	19950607
CA 2192797	AA	19961219	CA 1996-2192797	19960605
EP 934931	A2	19990811	EP 1999-103667	19960605
EP 934931	A3	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000026412	A2	20000125	JP 1999-159567	19960605
ES 2159741	T3	20011016	ES 1996-918093	19960605
JP 3231044	B2	20011119	JP 1997-501363	19960605
US 6316635	B1	20011113	US 1999-293518	19990415
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2002102608	A1	20020801	US 2001-897755	20010703
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1995-485323	A2	19950607
EP 1996-918093	A3	19960605
JP 1997-501363	A3	19960605
US 1996-655223	A2	19960605
US 1996-655224	A2	19960605
US 1996-655226	A2	19960605
US 1996-655255	B2	19960605
US 1996-659191	A1	19960605
US 1996-702232	B1	19960823
US 1997-915366	A3	19970820
US 1998-82056P	P	19980416
US 1998-212494	A2	19981215
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 129:175549

GI



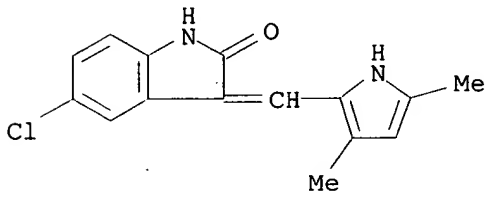
I

AB Title compds. [I; R1 = H or alkyl; R2 = (un)substituted (hetero)aryl; R4-R7 = H, halo, alkyl, alkoxy, etc.; X = O or S] were prepd. Thus, oxindole was condensed with 4-pyridinecarboxaldehyde to give I (R1,R4-R7 = H, R2 = 4-pyridinyl, X = O). Data for biol. activity of I were given.

IT **186611-56-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-(hetero)arylmethylene-2-indolinones as tyrosine kinase signal transduction modulators)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:140244 HCAPLUS
DOCUMENT NUMBER: 126:139901
TITLE: Indolinone compounds capable of modulating tyrosine kinase signal transduction
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9640116 A1 19961219 WO 1996-US8903 19960605
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
US 5880141 A 19990309 US 1995-485323 19950607
CA 2192797 AA 19961219 CA 1996-2192797 19960605
AU 9660441 A1 19961230 AU 1996-60441 19960605
AU 706597 B2 19990617
EP 769947 A1 19970502 EP 1996-918093 19960605
EP 769947 B1 20010502
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
BR 9606410 A 19971230 BR 1996-6410 19960605
JP 10504323 T2 19980428 JP 1996-501363 19960605
EP 934931 A2 19990811 EP 1999-103667 19960605
EP 934931 A3 19991020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI
JP 2000026412 A2 20000125 JP 1999-159567 19960605
AT 200863 E 20010515 AT 1996-918093 19960605
ES 2159741 T3 20011016 ES 1996-918093 19960605
JP 3231044 B2 20011119 JP 1997-501363 19960605
NO 9605377 A 19970212 NO 1996-5377 19961213
HK 1011933 A1 20020118 HK 1998-113193 19981211
US 2002022626 A1 20020221 US 2000-617529 20000713
US 2003108946 A1 20030612 US 2002-76621 20020219

PRIORITY APPLN. INFO.:
US 1995-485323 A 19950607
EP 1996-918093 A3 19960605
JP 1997-501363 A3 19960605
WO 1996-US8903 W 19960605
US 1997-915366 A3 19970820
US 2000-617529 B1 20000713

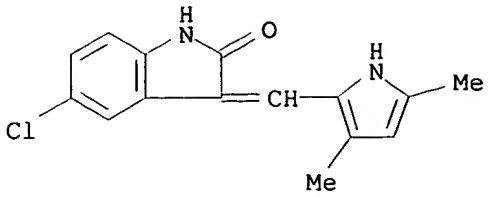
OTHER SOURCE(S): MARPAT 126:139901

AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

IT **186611-56-3P**, SU 5614
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indolinones capable of modulating tyrosine kinase signal transduction)

RN 186611-56-3 HCAPLUS

CN 2H-Indol-2-one, 5-chloro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)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WEST

End of Result Set

☐ Generate Collection Print

L26: Entry 3 of 3 File: USPT Dec 3, 1996

DOCUMENT-IDENTIFIER: US 5580722 A
TITLE: Methods of determining chemicals that modulate transcriptionally expression of genes associated with cardiovascular disease

Abstract Text (1):
The invention provided for a method of directly and specifically transcriptionally modulating the expression of a gene encoding a protein of interest associated with treatment of one or more symptoms of a cardiovascular disease such as atherosclerosis, restenosis or hypertension.

Application Filing Date (1):
19920207

Detailed Description Text (46):
In the methods described above the cardiovascular disease may be associated with thrombosis. In these cases the protein of interest may be one of the following: fibrinogen, fibrinogen receptor subunit IIb, fibrinogen receptor subunit IIIa, fibrinogen receptor subunit .beta..sub.3, fibrinogen receptor subunit .alpha..sub.v, von Willebrand factor (vWF), vWF receptor subunit Ib.beta., vWF receptor subunit Ib.alpha., vWF receptor subunit GPIX, plasminogen activator-1, platelet activating factor receptor, plasminogen, tissue plasminogen activator t-PA, u-PA, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, protein C, protein S, thrombomodulin, tissue factor, thrombospondin, CD36, kininogen, an eicosanoid receptor or an eicosanoid biosynthetic enzyme.

L11 ANSWER 51 OF 51 MEDLINE on STN DUPLICATE 34
ACCESSION NUMBER: 93063297 MEDLINE
DOCUMENT NUMBER: 93063297 PubMed ID: 1279432
TITLE: Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo.
AUTHOR: Plate K H; Breier G; Weich H A; Risau W
CORPORATE SOURCE: Max-Planck-Institut fur Psychiatrie, Martinsried, Germany.
SOURCE: NATURE, **(1992 Oct 29)** 359 (6398) 845-8.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19960129
Entered Medline: 19921201

AB Clinical and experimental studies suggest that angiogenesis is a prerequisite for solid tumour growth. Several growth factors with mitogenic or chemotactic activity for endothelial cells in vitro have been described, but it is not known whether these mediate tumour vascularization in vivo. Glioblastoma, the most common and most malignant brain tumour in humans, is distinguished from astrocytoma by the presence of necroses and vascular proliferations. Here we show that expression of an endothelial cell-specific mitogen, vascular endothelial growth factor (VEGF), is induced in astrocytoma cells but is dramatically upregulated in two apparently different subsets of glioblastoma cells. The high-affinity tyrosine kinase receptor for **VEGF**, **flt**, although not expressed in normal brain endothelium, is upregulated in **tumour** endothelial cells in vivo. These observations strongly support the concept that tumour angiogenesis is regulated by paracrine mechanisms and identify VEGF as a potential tumour angiogenesis factor in vivo.

L11 ANSWER 48 OF 51 CANCERLIT on STN
ACCESSION NUMBER: 96605260 CANCERLIT
DOCUMENT NUMBER: 96605260
TITLE: Regulation of glioma angiogenesis (Meeting abstract).
AUTHOR: Plate K H; Millauer B; Breier G; Shawver L; Ullrich A; Risau W
CORPORATE SOURCE: MPI, 61231 Bad Nauheim.
SOURCE: Br J Cancer, **(1994)** 71 (Suppl 24) 3.
ISSN: 0007-0920.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB Angiogenesis, the sprouting of capillaries from preexisting vessels, is observed during normal physiological processes, eg, embryonic development, and also occurs during solid **tumor** growth. We have studied the expression of vascular endothelial growth factor (VEGF) and its cognate tyrosine kinase receptors **flt**-1/**VEGF** receptor-1 and flk-1/KDR/VEGF receptor-2 during normal brain development and glioma-induced angiogenesis. To inhibit **tumor** angiogenesis in vivo, a retrovirus encoding a signaling defective flk-1/VEGFR-2 mutant was constructed. Our results suggest a paracrine control of angiogenesis and endothelial cell proliferation which is tightly regulated and transient in the embryonic brain, switched off in the normal adult brain and turned on in **tumor** cells (**VEGF**) and the host vasculature (**flt**-1 and flk-1/KDR) during **tumor** progression. The pattern is indistinguishable in human glioblastoma and a rat cerebral transplantation model using C6 or GS-9L glioma cells. Glioma growth initiated by grafting of **tumor** cells into nude mice or syngeneic rats could be significantly inhibited by gene transfer of a signalling-defective flk-1 receptor into endothelial cells in situ. Our studies identify VEGF as a **tumor** angiogenesis factor in human and rodent glial **tumors** and the VEGF/flk-1 system as a possible target in **tumor** therapy.

L11 ANSWER 43 OF 51 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 95098237 MEDLINE
DOCUMENT NUMBER: 95098237 PubMed ID: 7528359
TITLE: Detection and quantification of vascular endothelial growth factor/vascular permeability factor in brain tumor tissue and cyst fluid: the key to angiogenesis?.
AUTHOR: Weindel K; Moringlane J R; Marme D; Weich H A
CORPORATE SOURCE: Institute of Molecular Medicine, Albert-Ludwigs-University, Freiburg, Germany.
SOURCE: NEUROSURGERY, **(1994 Sep)** 35 (3) 439-48; discussion 448-9.
Journal code: 7802914. ISSN: 0148-396X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19970203
Entered Medline: 19950126

AB In primary malignant brain tumors increased vascularity and marked edema strongly suggest a possible role of the vascular endothelial growth factor/vascular permeability factor (VEGF/VPF). This was confirmed by earlier in situ hybridization studies, by analysis of the expression of the mitogen in different subsets of glioblastoma cells, and by the fact that the **VEGF**/VPF receptor **flt**-1 (fms-like tyrosine kinase) is up-regulated in **tumor** cells in vivo. To assess and quantify the expression of the VEGF/VPF gene and of the receptor gene, 26 surgical specimens of brain tumor tissue from 24 patients were analyzed. In most malignant gliomas, the expression level of the VEGF/VPF gene is elevated and can be increased up to 20- to 50-fold in comparison with low-grade tumors. Using polymerase chain reaction-based amplification, it could be shown that the messenger RNAs of three different VEGF/VPF forms are synthesized in tumor tissue samples. Northern blot studies revealed that in some samples a significant expression of the gene coding for placenta growth factor, a growth factor closely related to VEGF/VPF, was observed. In addition, using a radioreceptor assay it was possible to detect high VEGF/VPF-like activity in the cyst fluids of brain tumors, indicating the accumulation of the mitogen and permeability factor in brain tumor cysts. Further investigations revealed that astrocytoma and glioblastoma cells in culture express the VEGF/VPF gene and secrete the VEGF/VPF protein, whereas gene expression of the two known VEGF/VPF receptors, kinase insert domain-containing receptor and flt-1, could not be detected. These data support previous reports, which stated that VEGF/VPF acts as a paracrine growth and permeability factor in brain tumors and may contribute to tumor growth by initiating tumor angiogenesis.

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L3: Entry 1 of 1 File: USPT Mar 9, 1999

DOCUMENT-IDENTIFIER: US 5880141 A
TITLE: Benzylidene-Z-indoline compounds for the treatment of disease

US Patent No. (1):
5880141

Detailed Description Text (14):
The compounds described above may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry.

Detailed Description Text (55):
A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD.sub.50 (the dose lethal to 50% of the population) and the ED.sub.50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD.sub.50 and ED.sub.50. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED.sub.50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).

Detailed Description Text (421):
Day X: Data analysis--Find averages and standard deviations for each set of four OD's.

Detailed Description Text (458):
Therapeutic compounds should be more potent in inhibiting receptor tyrosine kinase activity than in exerting a cytotoxic effect. A measure of the effectiveness and cell toxicity of a compound can be obtained by determining the therapeutic index: IC.sub.50 /LD.sub.50. IC.sub.50, the dose required to achieve 50% inhibition, can be measured using standard techniques such as those described herein. LD.sub.50, the dosage which results in 50% toxicity, can also be measured by standard techniques (Mossman, 1983, J. Immunol. Methods, 65:55-63), by measuring the amount of LDH released (Korzeniewski and Callewaert, 1983, J. Immunol. Methods 64:313; Decker and Lohmann-Matthes, 1988, J. Immunol. Methods 115:61), or by measuring the lethal dose in animal models. Compounds with a large therapeutic index are preferred. The therapeutic index should be greater than 2, preferably at least 10, more preferably at least 50.

Detailed Description Text (477):
For the rat IC model, rats (Wistar, Sprague Dawley, Fisher 344, or athymic R/Nu; approximately 200 g) were anesthetized by an IP injection of 100 mg/kg Ketaset

ketamine hydrochloride; Aveco, Fort Dodge, Iowa) and 5 mg/kg Rompun (xylazine, 2% solution; Bayer, Germany). After onset of anesthesia, the scalp was shaved and the animal was oriented in a stereotaxic apparatus (Stoelting, Wood Dale, Ill.). The skin at the incision site was cleaned 3 times with alternating swabs of 70% ethanol and 10% Poidone-Iodine. A median 1.0-1.5 cm incision was made in the scalp using a sterile surgical blade. The skin was detached slightly and pulled to the sides to expose the sutures on the skull surface. A dental drill (Stopiting, Wood Dale, Ill.) was used to make a small (1-2 mm diameter) burrhole in the skull approximately 1 mm anterior and 2 mm lateral to the bregma. The cell suspension was drawn into a 50 .mu.L Hamilton syringe fitted with a 23 or 25 g a standard bevel needle. The syringe was oriented in the burrhole at the level of the arachnoidea and lowered until the tip of the needle was 3 mm deep into the brain structure, where the cell suspension was slowly injected. After cells were injected, the needle was left in the burrhole for 1-2 minutes to allow for complete delivery of the cells. The skull was cleaned and the skin was closed with 2 to 3 sutures. Animals were observed for recovery from surgery and anesthesia. Throughout the experiment, animals were observed at least twice each day for development of symptoms associated with progression of intracerebral tumor. Animals displaying advanced symptoms (leaning, loss of balance, dehydration, loss of appetite, loss of coordination, cessation of grooming activities, and/or significant weight loss) were humanely sacrificed and the organs and tissues of interest were resected.

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End of Result Set

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L4: Entry 1 of 1 File: USPT Mar 9, 1999

DOCUMENT-IDENTIFIER: US 5880141 A
TITLE: Benzylidene-Z-indoline compounds for the treatment of disease

US Patent No. (1):
5880141

Brief Summary Text (11):
A second family of RTKs, designated the insulin subfamily, is comprised of the INS-R, the IGF-1R and the IR-R. A third family, the "PDGF" subfamily includes the PDGF .alpha. and .beta. receptors, CSFIR, c-kit and FLK-II. Another subfamily of RTKs, identified as the FLK family, is believed to be comprised of the Kinase insert Domain-Receptor fetal liver kinase-1 (KDR/FLK-1), the fetal liver kinase 4 (FLK-4) and the fms-like tyrosine kinase 1 (flt-1). Each of these receptors was initially believed to be receptors for hematopoietic growth factors. Two other subfamilies of RTKs have been designated as the FGF receptor family (FGFR1, FGFR2, FGFR3 and FGFR4) and the Met subfamily (c-met and Ron).

Brief Summary Text (12):
Because of the similarities between the PDGF and FLK subfamilies, the two subfamilies are often considered together. The known RTK subfamilies are identified in Plowman et al., 1994, DN&P 7(6) :334-339, which is incorporated herein by reference.

Detailed Description Text (82):
6.1.1. FLK-1 ELISA

Detailed Description Text (83):
An ELISA assay was conducted to measure the kinase activity of the FLK-1 receptor and more specifically, the inhibition or activation of protein tyrosine kinase activity on the FLK-1 receptor. Specifically, the following assay was conducted to measure kinase activity of the FLK-1 receptor in FLK-1/NIH3T3 cells.

Detailed Description Text (96):
k. NIH3T3 C7#3 Cells (FLK-1 expressing cells);

Detailed Description Text (101):
p. Affinity purified anti-FLK-1 antiserum, Enzymology Lab, Sugen, Inc.;

Detailed Description Text (469):
Assay 2: FLK-1/Xenograft Model.

Detailed Description Text (480):
In the following example, the Pellet Model was used in connection with testing a compound's activity against the FLK-1 receptor. More specifically, in order to determine the whether a compound is an effective FLK-1 inhibitor to disorders associated with the presence of VEGF, and more specifically, whether a compound may effectively inhibit the formation of blood vessels, a VEGF pellet model for designed. In this model, VEGF is packaged into a time-release pellet and implanted subcutaneously on the abdomen of nude mice to induce a `reddening` response and subsequent swelling around the pellet. Potential FLK-1 inhibitors may then be implanted in methylcellulose near the VEGF pellet ito determine whether such

inhibitor may be used to inhibit the "reddening" response and subsequent swelling.

Detailed Description Paragraph Table (24):

TABLE 1

ELISA Assay Results	HER-2	HER-2	FLK-1	Comp.	IGF-IR	IR	EGFR	PDGRF	BT474	3T3	Cell.
FLK-1											A
>100	>100	7.5	>100	77	1	0.02	B	8	19	11	14
28	18	C	>100	>100	>100	10	>100	1	0.01		

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End of Result Set

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L2: Entry 1 of 1 File: USPT Mar 9, 1999

DOCUMENT-IDENTIFIER: US 5880141 A
TITLE: Benzylidene-Z-indoline compounds for the treatment of disease

US Patent No. (1):
5880141

Brief Summary Text (7):
Aberrant expression or mutations in the PTKs have been shown to lead to either uncontrolled cell proliferation (e.g. malignant tumor growth) or to defects in key developmental processes. Consequently, the biomedical community has expended significant resources to discover the specific biological role of members of the PTK family, their function in differentiation processes, their involvement in tumorigenesis and in other diseases, the biochemical mechanisms underlying their signal transduction pathways activated upon ligand stimulation and the development of novel drugs.

Brief Summary Text (14):
Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways leading to cellular signal assays signalling pathways leading to pathogenic conditions, including cancer, psoriasis and hyper immune response.

Brief Summary Text (15):
Development Of Compounds To Modulate The PTKs. In view of the surmised importance of PTKs to the control, regulation and modulation of cell proliferation and the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. application Ser. No. 4,966,849), soluble receptors and antibodies (Application No. WO 94/10202; Kendall & Thomas, 1994, Proc. Nat'l Acad. Sci 90:10705-09; Kim, et al., 1993, Nature 362:841-844), RNA ligands (Jellinek, et al., Biochemistry 33:10450-56); Takano, et al., 1993, Mol. Bio. Cell 4:358A; Kinsella, et al., 1992, Exp. Cell Res. 199:56-62; Wright, et al., 1992, J. Cellular Phys. 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Pat. No. 5,330,992; Mariani, et al., 1994, Proc. Am. Assoc. Cancer Res. 35:2268).

Brief Summary Text (16):
More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642), vinylene-azaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Pat. No. 5,330,992) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer.

Brief Summary Text (24):
More particularly, the compositions of the present invention may be included in methods for treating diseases comprising proliferation or metabolic disorders, for

example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy.

Detailed Description Text (5):
Tyrosine kinase signal transduction results in, among other responses, cell proliferation, differentiation and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

Detailed Description Text (6):
This invention is therefore directed to compounds which regulate, modulate and/or inhibit disorders associated with abnormal cell proliferation by affecting the enzymatic activity of the RTKs and/or the non-receptor tyrosine kinases and interfering with the signal transduced such proteins. More particularly, the present invention is directed to compounds which regulate, modulate and/or inhibit the RTK and/or non-receptor tyrosine kinase mediated signal transduction pathways as a therapeutic approach to cure leukemia and many kinds of solid tumors, including but not limited to carcinoma, sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

Detailed Description Text (17):
Cell proliferative disorders which can be treated or further studied by the present invention include cancers, blood vessel proliferative disorders, fibrotic disorders, and mesangial cell proliferative disorders.

Detailed Description Text (18):
Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

Detailed Description Text (20):
Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The PDGF-R has been implicated in the maintenance of mesangial cell proliferation. Floege et al., 1993, Kidney International 43:547-554.

Detailed Description Text (22):
PTKs have been associated with such cell proliferative disorders. For example, some members of the RTK family have been associated with the development of cancer. Some of these receptors, like the EGFR (Tuzi et al., 1991, Br. J. Cancer 63:227-233; Torp et al., 1992, APMIS 100:713-719) HER2/neu (Slamon et al., 1989, Science 244:707-712) and the PDGF-R (Kumabe et al., 1992, Oncogene 7:627-633) are overexpressed in many tumors and/or persistently activated by autocrine loops. In fact, in the most common and severe cancers these receptor overexpressions (Akbasak and Sunar-Akbasak., 1992, J. Neurol. Sci. 111:119-133; Dickson et al., 1992, Cancer Treatment Res. 61:249-273; Korc et al., 1992, J. Clin. Invest. 90:1352-1360) and autocrine loops (Lee and Donoghue, 1992, J. Cell. Biol. 118:1057-1070; Korc et al., supra; Akbasak and Sunar-Akbasak., supra) have been demonstrated. For example, the EGFR receptor has been associated with squamous cell carcinoma, astrocytoma, glioblastoma, head and neck cancer, lung cancer and bladder cancer. HER2 has been associated with breast,

ovarian, gastric, lung, pancreas and bladder cancer. The PDGF-R has been associated with glioblastoma, lung, ovarian, melanoma and prostate cancer. The RTK c-met has been generally associated with hepatocarcinogenesis and thus hepatocellular carcinoma. Additionally, c-met has been linked to malignant tumor formation. More specifically, the RTK c-met has been associated with, among other cancers, colorectal, thyroid, pancreatic and gastric carcinoma, leukemia and lymphoma. Additionally, over-expression of the c-met gene has been detected in patients with Hodgkins disease, Burkitts disease, and the lymphoma cell line.

Detailed Description Text (23):
The IGF-IR, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-I has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteaga et al., 1989, J. Clin. Invest. 84:1418-1423) and small lung tumor cells (Macauley et al., 1990, Cancer Res. 50:2511-2517). In addition, IGF-I, integrally involved in the normal growth and differentiation of the nervous system, appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., 1993, Cancer Res. 53:2475-2478. The importance of the IGF-IR and its ligands in cell proliferation is further supported by the fact that many cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes, osteoblasts, the stem cells of the bone marrow) are stimulated to grow by IGF-I. Goldring and Goldring, 1991, Eukaryotic Gene Expression 1:301-326. In a series of recent publications, Baserga even suggests that IGF-I-R plays a central role in the mechanisms of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies. Baserga, 1995, Cancer Res. 55:249-252; Baserga, 1994, Cell 79:927-930; Coppola et al., 1994, Mol. Cell. Biol. 14:4588-4595.

Detailed Description Text (24):
The association between abnormalities in RTKs and disease are not restricted to cancer, however. For example, RTKs have been associated with metabolic diseases like psoriasis, diabetes mellitus, wound healing, inflammation, and neurodegenerative diseases. For example, the EGF-R is indicated in corneal and dermal wound healing. Defects in the Insulin-R and the IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., 1994, DN&P 7:334-339.

Detailed Description Text (25):
Not only receptor type tyrosine kinases, but also many cellular tyrosine kinases (CTKs) including src, abl, fps, yes, fyn, lyn, lck, blk, hck, fgr, yrk (reviewed by Bolen et al., 1992, FASEB J. 6:3403-3409) are involved in the proliferative and metabolic signal transduction and thus in indications of the present invention. For example, mutated src (v-src) has been demonstrated as an oncoprotein (pp60.sup.v-src) in chicken. Moreover, its cellular homolog, the proto-oncogene pp60.sup.c-src transmits oncogenic signals of many receptors. For example, overexpression of EGF-R or HER2/neu in tumors leads to the constitutive activation of pp60.sup.c-src, which is characteristic for the malignant cell but absent from the normal cell. On the other hand, mice deficient for the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders. Similarly, Zap 70 is implicated in T-cell signalling.

Detailed Description Text (32):
Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation.

Detailed Description Text (33):
Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

Detailed Description Text (61):
The compositions may, if desired, be presented in a pack or dispenser device which

may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

Detailed Description Text (102):
q. UB40 monoclonal antibody specific for phosphotyrosine, Enzymology Lab, Sugen, Inc. (see, Fendly, et al., 1990, Cancer Research 50:1550-1558);

Detailed Description Text (172):
a. BT-474 (ATCC HBT20), a human breast tumor cell line which expresses high levels of HER2 kinase.

Detailed Description Text (363):
Assay 2: PDGF-R/SRB Adherent Cells Growth Assay. Compounds were tested for inhibition of anchorage-dependent tumor cell growth using the calorimetric assay described by Skehan et al., 1990. J. Natl. Cancer Inst. 82:1107-1112. The assay measures protein content of acid-fixed cells using the counterion binding dye sulforhodamine B (SRB, Sigma). The compounds were solubilized in DMSO (Sigma, cell culture grade) and diluted into appropriate growth medium at two-fold the desired final assay concentration. In assays using C6 cells, compounds (100 .mu.l) were added to 96-well plates containing attached cellular monolayers (2000 cells/well in 100 .mu.l). C6 cells were maintained in Ham's F10 supplemented with 5% fetal bovine serum (FBS) and 2 mM glutamine (GLN). After 4 days (37.degree. C., 5% CO.sub.2) the monolayers were washed 3 times with PBS and fixed with 200 .mu.l ice-cold 10% TCA (Fisher Scientific), and kept at 4.degree. C. for 60 min. The TCA was removed and the fixed monolayers were washed 5 times with tap water and allowed to dry completely at room temperature on absorbent paper. The cellular protein was stained for 10 min with 100 .mu.l 0.4% SRB dissolved in 1% acetic acid. After 5 washes with tap water, the dye was solubilized in 10 mM Tris base (100 .mu.l per well) and absorbance read at 570 nm on a Dynatech plate reader model MR5000. Growth inhibition data are expressed as a percentage of absorbance detected in control wells which were treated with 0.4% DMSO alone. DMSO controls were not different from cells grown in regular growth medium. IC.sub.50 values were determined using a four parameter curve fit function.

Detailed Description Text (364):
For the anchorage-independent tumor cell growth assay, cells (3000 to 5000 per dish) suspended in 0.4% agarose in assay medium (DMEM containing 10% FCS) with and without Compounds were plated into 35 mm dishes coated with a solidified agarose base layer (0.8% agarose). After a 2 to 3 week incubation at 37.degree. C., colonies larger than 50 .mu.m were quantified using an Omnicon 3800 Tumor Colony counter.

Detailed Description Text (432):
Growth assays were carried out using human mammary epithelial SKBR3 (ATCC HTB30) cells, SKOV3 (ATCC HTB77) human ovarian cancer cell line, A431 cells, MCF7 human breast carcinoma cells, MCF7 cells overexpress the HER2 kinase (MCF7-HER2), NIH3T3 cells, and NIH3T3 cells overexpressing the HER2 kinase (3T3-HER2)

Detailed Description Text (461):
The ability of human tumors to grow as xenografts in athymic mice (e.g., Balb/c, nu/nu) provides a useful in vivo model for studying the biological response to therapies for human tumors. Since the first successful xenotransplantation of human tumors into athymic mice, (Rygaard and Povlsen, 1969, Acta Pathol. Microbial. Scand. 77:758-760), many different human tumor cell lines (e.g., mammary, lung, genitourinary, gastrointestinal, head and neck, glioblastoma, bone, and malignant melanomas) have been transplanted and successfully grown in nude mice. Human mammary tumor cell lines, including MCF-7, ZR75-1, and MDA-MB-231, have been established as subcutaneous xenografts in nude mice (Warri et al., 1991, Int. J. Cancer 49:616-623; Ozzello and Sordat, 1980, Eur. J. Cancer 16:553-559; Osborne et al., 1985, Cancer Res. 45:584-590; Seibert et al., 1983, Cancer Res. 43:2223-2239).

Detailed Description Text (463):
To study the effect of anti-tumor drug candidates on HER2 expressing tumors, the tumor cells should be able to grow in the absence of supplemental estrogen. Many mammary cell lines are dependent on estrogen for in vivo growth in nude mice (Osborne et al., supra), however, exogenous estrogen suppresses HER2 expression in nude mice (Warri et al., supra, Dati et al., 1990, Oncogene 5:1001-1006). For example, in the presence of estrogen, MCF-7, ZR-75-1, and T47D cells grow well in viva, but express very low levels of HER2 (Warri et al., supra, Dati et al., supra).

Detailed Description Text (465):
1) implant tumor cells (subcutaneously) into the hindflank of five- to six-week-old female Balb/c nu/nu athymic mice;

Detailed Description Text (466):
2) administer the anti-tumor compound;

Detailed Description Text (467):
3) measure tumor growth by measuring tumor volume.

Detailed Description Text (468):
The tumors can also be analyzed for the presence of a receptor, such as HER2, EGF or PDGF, by Western and immunohistochemical analyses. Using techniques known in the art, one skilled in the art can vary the above procedures, for example through the use of different treatment regimes.

Detailed Description Text (470):
The ability of the compounds of the present invention to inhibit ovarian, melanoma, prostate, lung and mammary tumor cell lines established as SC xenografts was examined. These studies were conducted using doses ranging from 12 to 20 mg/kg/day.

Detailed Description Text (471):
Materials And Methods. The tumor cells were implanted subcutaneously into the indicated strains of mice. Treatment was initiated on day 1 post implantation unless otherwise indicated (e.g. treatment of the SCID mouse related to the A375 melanoma cell line began on Day 9). Eight (8) to ten (10) mice comprised each test group.

Detailed Description Text (475):
Subcutaneous Xenograft Model. Cell lines were grown in appropriate medium as described (See Section 6). Cells were harvested at or near confluency with 0.05% Trypsin-EDTA and pelleted at 450.times.g for 10 min. Pellets were resuspended in sterile PBS or media (without FBS) to a suitable concentration indicated in the Figure legends and the cells were implanted into the hindflank of mice. Tumor growth was measured over 3 to 6 weeks using venier calipers and tumor volumes were calculated as a product of length.times.width.times.height unless otherwise indicated. P values were calculated using the Students' t-test. su101 in 50-100 .mu.L excipient (dimethylsulfoxide, PBTE, PBTE6C:D5W, or PBTE:D5W) was delivered by IP injection at concentrations indicated in the Figure legends.

Detailed Description Text (477):
For the rat IC model, rats (Wistar, Sprague Dawley, Fisher 344, or athymic R/Nu; approximately 200 g) were anesthetized by an IP injection of 100 mg/kg Ketaset (ketamine hydrochloride; Aveco, Fort Dodge, Iowa) and 5 mg/kg Rompun (xylazine, 2% solution; Bayer, Germany). After onset of anesthesia, the scalp was shaved and the animal was oriented in a stereotaxic apparatus (Stoelting, Wood Dale, Ill.). The skin at the incision site was cleaned 3 times with alternating swabs of 70% ethanol and 10% Poidone-Iodine. A median 1.0-1.5 cm incision was made in the scalp using a sterile surgical blade. The skin was detached slightly and pulled to the sides to expose the sutures on the skull surface. A dental drill (Stopiting, Wood Dale, Ill.) was used to make a small (1-2 mm diameter) burrhole in the skull approximately 1 mm anterior and 2 mm lateral to the bregma. The cell suspension was drawn into a 50 .mu.L Hamilton syringe fitted with a 23 or 25 g a standard bevel needle. The syringe was oriented in the burrhole at the level of the arachnoidea and lowered until the tip of the needle was 3 mm deep into the brain structure, where the cell suspension

was slowly injected. After cells were injected, the needle was left in the burrhole for 1-2 minutes to allow for complete delivery of the cells. The skull was cleaned and the skin was closed with 2 to 3 sutures. Animals were observed for recovery from surgery and anesthesia. Throughout the experiment, animals were observed at least twice each day for development of symptoms associated with progression of intracerebral tumor. Animals displaying advanced symptoms (leaning, loss of balance, dehydration, loss of appetite, loss of coordination, cessation of grooming activities, and/or significant weight loss) were humanely sacrificed and the organs and tissues of interest were resected.

Detailed Description Text (478):
Intraperitoneal Model. Cell lines were grown in the appropriate media. Cells were harvested and washed in sterile PBS or medium without FBS, resuspended to a suitable concentration, and injected into the IP cavity of mice of the appropriate strain. Mice were observed daily for the occurrence of ascites formation. Individual animals were sacrificed when they presented with a weight gain of 40%, or when the IP tumor burden began to cause undue stress and pain to the animal.

Detailed Description Text (506):
Because of the established role played by many of the RTKs, e.g., the HER2 receptor, in breast cancer, the mammary fat pad model is particularly useful for measuring the efficacy of compounds which inhibit such RTKs. By implanting tumor cells directly into the location of interest, in situ models more accurately reflect the biology of tumor development than do subcutaneous models. Human mammary cell lines, including MCF-7, have been grown in the mammary fat pad of athymic mice. Shafie and Grantham, 1981, Natl. Cancer Instit. 67:51-56; Gottardis et al., 1988, J. Steroid Biochem. 30:311-314. More specifically, the following procedure can be used to measure the inhibitory effect of a compound on the HER2 receptor:

Detailed Description Text (509):
3) Measure the tumor growth at various time points.

Detailed Description Text (510):
The tumors can also be analyzed for the presence of a receptor such as HER2, by Western and immunohistochemical analyses. Using techniques known in the art, one skilled in the art can vary the above procedures, for example through the use of different treatment regimes.

Other Reference Publication (27):
Shiraishi, T., Owada, M. K., Tatsuka, M., Yamashita, T., Watanabe, K., and Kakunaga, T. (1989). Specific inhibitors of tyrosine-specific protein kinases: properties of 4-hydroxycinnamamide derivates in vitro. Cancer Research 49, 2374-78.

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Kobayashi, G., Y. Matsuda, Y. Tominaga, M. Ohkuma, H. Shinoda, M. Kohno, and D. i. Mizuno. 1977. Anti-tumor activity of indole derivatives. Yakugaku Zasshi 97:1033-.

Other Reference Publication (64):
Akbasak, A., and Sunar-Akbasak, B. (1992). Oncogenes: cause or consequence in the development of glial tumors. Journal of Neurological Sciences 111, 119-133.

Other Reference Publication (65):
Arteaga, C. L., Kitten, L. J., Coronado, E. B., Jacobs, S., Kull, F. C. J., Allred, D. C., and Osborne, C. K. (1989). Blockade of the type I somatomedin receptor inhibits growth of human breast cancer cells in athymic mice. J. Clin. Invest. 84, 1418-1423.

Other Reference Publication (67):
Baserga, R. (1995). The insulin-like growth factor I receptor: a key to tumor growth? Cancer Research 55, 249-252.

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Dati, C., Antoniotti, S., Taverna, D., Perroteau, I., and De Bortoli, M. (1990). Inhibition of c-erB-2 oncogene expression by estrogens in human breast cancer cells. Oncogene 5, 1001-1006.

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Decker, T., and Lohmann-Matthes, M.-L. (1988). A quick and simple method for quantitation of lactate dehydrogenase release in measurements of cellular cytotoxicity and tumor necrosis factor (TNF) activity. J. of Imm. Methods 15, 61-69.

Other Reference Publication (73):
Dickson, R. B., Salomon, D. S., and Lippman, M. E. (1991). Tyrosine kinase receptor--nuclear protooncogene interactions in breast cancer. Cancer Treatment and Research 61, 249-273.

Other Reference Publication (75):
Fendly, B. M. (1990). Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. Cancer Research 50, 1550-1558.

Other Reference Publication (79):
Gottardis, M. M., Robinson, S. P., and Jordan, C. V. (1988). Estradiol-stimulated growth of MCF-7 tumors implanted in athymic mice: A model to study the tumoristatic action of tamoxifen. J. Steriod Biochem. 30, 311-314.

Other Reference Publication (86):
Korc, M., et al. (1992). Overexpression of the epidermal growth factor receptor in human pancreatic cancer is associated with concomitant increases in the levels of epidermal growth factor and transforming growth factor alpha. J. Clin. Inv. 90, 1352-60.

Other Reference Publication (88):
Kumabe, T., et al. (1992). Amplification of alpha-platelet-derived growth factor receptor gene lacking an exon coding for a portion of the extracellular region in a primary brain tumor of glial origin. Oncogene 7, 627-633.

Other Reference Publication (90):
Macaulay, V. M., Everard, M. J., Teale, J. D., Trott, P. A., Van Wyk, J. J., and Smith, I. E. (1990). Autocrine function for insulin-like growth factor I in human small cell lung cancer cell lines and fresh tumor cells. Cancer Research 50, 2511-2517.

Other Reference Publication (91):
Mariani, M., et al. (1994). Inhibition of angiogenesis by PCE26806, a potent tyrosine kinase inhibitor. Proceedings of the American Association for Cancer Research 35, 381.

Other Reference Publication (93):
Osborne, C. K., Hobbs, K., and Clark, G. M. (1985). Effect of estrogens and antiestrogens on growth of human breast cancer cells in athymic nude mice. Cancer Research 45, 584-590.

Other Reference Publication (94):
Ozzello, L., and Sordat, M. (1980). Behavior of tumors produced by transplantation of human mammary cell lines in athymic nude mice. Europ. J. Cancer 16, 553-559.

Other Reference Publication (96):
Rygaard, J., and Poulson, C. O. (1969). Heterotransplantation of a human malignant tumour to "nude" mice. Acta. path. microbiol scand. 77, 758-760.

Other Reference Publication (97):
Sandberg-Nordqvist, A.-C., Stahlbom, P.-A., Reinecke, M., Collins, P. V., von Holst, H., and Sara, V. (1993). Characterization of insulin-like growth factor 1 in human primary brain tumors. Cancer Research 53, 2475-2478.

Other Reference Publication (99):
Seibert, K., Shafie, S. M., Triche, T. J., Whang-Peng, J. J., O'Brien, S. J., Toney, J. H., Huff, K. K., and Lippman, M. E. (1983). Clonal variation of MCF-7 breast

cancer cells in vitro and in athymic nude mice. Cancer Research 43, 2223-2239.

Other Reference Publication (100):
Shafie, S. M., and Grantham, F. H. (1981). Role of hormones in the growth and regression of human breast cancer cells (MCF-7) transplanted into athymic nude mice. JNCI 67, 51-56.

Other Reference Publication (101):
Skehan, P., et al. (1990). New Colorimetric cytotoxicity assay for anticancer-drug screening. Journal of the National Cancer Institute 82, 1107-1112.

Other Reference Publication (102):
Slamon, D. J., et al. (1989). Studies of the HER-2/neu Proto-oncogene in Human Breast and Ovarian Cancer. Science 244, 707-712.

Other Reference Publication (106):
Torp, S. H., Helseth, E., Ryan, L., Stolan, S., Dalen, A., and Unsgaard, G. (1992). Expression of the epidermal growth factor receptor gene in human brain metastases. APMIS 100, 713-719.

Other Reference Publication (107):
Tuzi, N. L., Venter, D. J., Kumar, S., Staddon, S. L., Lemoine, N. R., and Gullick, W. J. (1990). Expression of growth factor receptors in human brain tumors. British J. of Cancer 63, 227-233.

Other Reference Publication (110):
Warri, A. M., et al. (1991). Estrogen suppression of erbB2 expression is associated with increased growth rate of ZR-75-1 human breast cancer cells in vitro and in nude mice. Int. J. Cancer 49, 616-623.

CLAIMS:

3. The method of claim 1 wherein said disease is selected from the group consisting of: cancer, blood vessel proliferative disorders, fibrotic disorders, mesangial cell proliferative disorders and metabolic diseases.

6. The method of claim 3 wherein the mesangial cell proliferative disorder is selected from the group consisting of glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies.

=> d ibib abs hitstr l16 1-2

L16 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:626172 HCAPLUS
DOCUMENT NUMBER: 131:257441
TITLE: Heterocyclic families of compounds [tricyclic-based indolinones and pyrazolecarboxylic acid amides] for the modulation of tyrosine protein kinase
INVENTOR(S): Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang, Congxin; McMahon, Gerald; Mohammadi, Moosa; Schlessinger, Joseph; Shawver, Laura K.; Sun, Li; Tang, Peng C.; Ullrich, Axel
PATENT ASSIGNEE(S): Sugen, Inc., USA; New York University; Max-Planck Institut fur Biochemie
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948868	A2	19990930	WO 1999-US6468	19990326
WO 9948868	A3	20000224		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2325935	AA	19990930	CA 1999-2325935	19990326
AU 9933635	A1	19991018	AU 1999-33635	19990326
EP 1066257	A2	20010110	EP 1999-915018	19990326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002507598	T2	20020312	JP 2000-537851	19990326
US 6514981	B1	20030204	US 1999-283657	19990401
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1998-79713P	P	19980326
US 1998-80422P	P	19980402
US 1998-81792P	P	19980415
US 1998-82056P	P	19980416
US 1998-89397P	P	19980615
US 1998-89521P	P	19980616
US 1998-98783P	P	19980901
US 1997-915366	A3	19970820
WO 1999-US6468	W	19990326
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 131:257441
GI

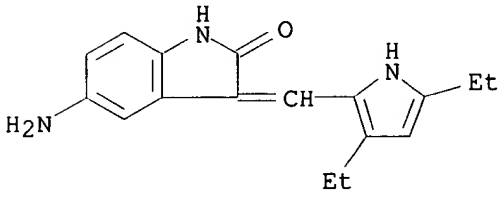
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

IT **204005-56-1P**, 5-Amino-3-[(3,5-diethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydroindol-2-one
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of pyrazolecarboxylic acid amides and (arylmethylene)indolinones as protein tyrosine kinase modulators)

RN 204005-56-1 HCAPLUS

CN 2H-Indol-2-one, 5-amino-3-[(3,5-diethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L16 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:147306 HCAPLUS

DOCUMENT NUMBER: 128:204803

TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease

INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus Peter; Shawver, Laura Kay; et al.

PATENT ASSIGNEE(S): Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald

SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

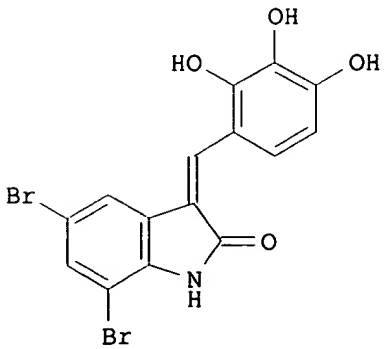
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807695	A1	19980226	WO 1997-US14736	19970820
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CN 1155838	A	19970730	CN 1996-190616	19960605
EP 929520	A1	19990721	EP 1997-939480	19970820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6147106	A	20001114	US 1997-915366	19970820
JP 2001503736	T2	20010321	JP 1998-510973	19970820
EP 1247803	A2	20021009	EP 2002-77564	19970820
EP 1247803	A3	20021016		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 9741556	A1	19980306	AU 1997-41556	19970821
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:

US 1996-702232	A	19960823
US 1996-31585P	P	19961205
US 1996-31586P	P	19961205
US 1996-31588P	P	19961205
US 1996-32546P	P	19961205
US 1996-32547P	P	19961205
US 1997-45565P	P	19970505
US 1997-45566P	P	19970505
US 1997-45714P	P	19970505
US 1997-45715P	P	19970505
US 1997-46843P	P	19970505
US 1996-45715P	P	19961205
US 1997-31565P	P	19970505
EP 1997-939480	A3	19970820
US 1997-915366	A3	19970820
WO 1997-US14736	W	19970820
US 2000-617529	B1	20000713

OTHER SOURCE(S): MARPAT 128:204803

GI



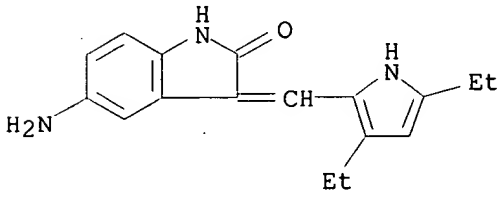
I

AB The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. The compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chem. substituents to the 3-[(indole-3-yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepd. by combinatorial condensation of certain (un)substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro.

IT **204005-56-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and testing of indolinone combinatorial library as protein kinase inhibitors)

RN 204005-56-1 HCAPLUS

CN 2H-Indol-2-one, 5-amino-3-[(3,5-diethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Compd. (h)

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L18 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:472477 HCAPLUS
DOCUMENT NUMBER: 135:56059
TITLE: Methods of modulating c-kit tyrosine protein kinase function with indolinone compounds
INVENTOR(S): Lipson, Ken; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

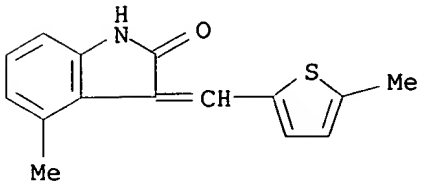
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045689	A2	20010628	WO 2000-US35009	20001222
WO 2001045689	A3	20020103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002010203	A1	20020124	US 2000-741842	20001222
EP 1255536	A2	20021113	EP 2000-991704	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 1999-171693P P 19991222
WO 2000-US35009 W 20001222
OTHER SOURCE(S): MARPAT 135:56059

AB The invention concerns indolinone compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders such as cancers characterized by over-activity or inappropriate activity of c-kit kinase.

IT **346405-31-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolinone derivs. for c-kit tyrosine protein kinase function modulation)

RN 346405-31-0 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-4-methyl-3-[(5-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



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L20 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:472477 HCAPLUS
DOCUMENT NUMBER: 135:56059
TITLE: Methods of modulating c-kit tyrosine protein kinase function with indolinone compounds
INVENTOR(S): Lipson, Ken; McMahon, Gerald
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045689	A2	20010628	WO 2000-US35009	20001222
WO 2001045689	A3	20020103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002010203	A1	20020124	US 2000-741842	20001222
EP 1255536	A2	20021113	EP 2000-991704	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

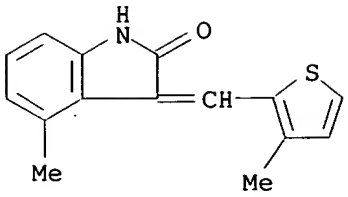
PRIORITY APPLN. INFO.: US 1999-171693P P 19991222
WO 2000-US35009 W 20001222

OTHER SOURCE(S): MARPAT 135:56059

AB The invention concerns indolinone compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders such as cancers characterized by over-activity or inappropriate activity of c-kit kinase.

IT **245036-26-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolinone derivs. for c-kit tyrosine protein kinase function modulation)

RN 245036-26-4 HCAPLUS
CN 2H-Indol-2-one, 1,3-dihydro-4-methyl-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



L20 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:626172 HCAPLUS
DOCUMENT NUMBER: 131:257441
TITLE: Heterocyclic families of compounds [tricyclic-based indolinones and pyrazolecarboxylic acid amides] for the modulation of tyrosine protein kinase
INVENTOR(S): Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang, Congxin; McMahon, Gerald; Mohammadi, Moosa; Schlessinger, Joseph; Shawver, Laura K.; Sun, Li; Tang, Peng C.; Ullrich, Axel
PATENT ASSIGNEE(S): Sugen, Inc., USA; New York University; Max-Planck Institut fur Biochemie
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948868	A2	19990930	WO 1999-US6468	19990326
WO 9948868	A3	20000224		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2325935	AA	19990930	CA 1999-2325935	19990326
AU 9933635	A1	19991018	AU 1999-33635	19990326
EP 1066257	A2	20010110	EP 1999-915018	19990326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002507598	T2	20020312	JP 2000-537851	19990326
US 6514981	B1	20030204	US 1999-283657	19990401
US 2002022626	A1	20020221	US 2000-617529	20000713
US 2003108946	A1	20030612	US 2002-76621	20020219

PRIORITY APPLN. INFO.:
US 1998-79713P P 19980326
US 1998-80422P P 19980402
US 1998-81792P P 19980415
US 1998-82056P P 19980416
US 1998-89397P P 19980615
US 1998-89521P P 19980616
US 1998-98783P P 19980901
US 1997-915366 A3 19970820

WO 1999-US6468 W 19990326
US 2000-617529 B1 20000713
OTHER SOURCE(S): MARPAT 131:257441
GI

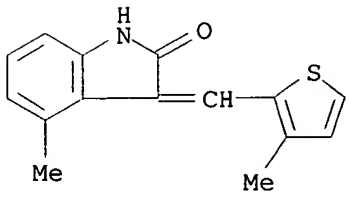
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

IT **245036-26-4P**, 4-Methyl-3-[(3-methylthiophen-2-yl)methylene]-1,3-dihydroindol-2-one
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of pyrazolecarboxylic acid amides and (arylmethylene)indolinones as protein tyrosine kinase modulators)

RN 245036-26-4 HCAPLUS

CN 2H-Indol-2-one, 1,3-dihydro-4-methyl-3-[(3-methyl-2-thienyl)methylene]- (9CI) (CA INDEX NAME)



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L22 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:117197 HCAPLUS
DOCUMENT NUMBER: 132:166123
TITLE: 3-Methylidenyl-2-indolinone modulators of protein kinase
INVENTOR(S): Tang, Peng Cho; Sun, Li; Miller, Todd Anthony; Liang, Congxin; Tran, Ngoc My; Nguyen, Anh Thi; Nematalla, Asaad
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 347 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008202	A2	20000217	WO 1999-US17845	19990804
WO 2000008202	A3	20000518		
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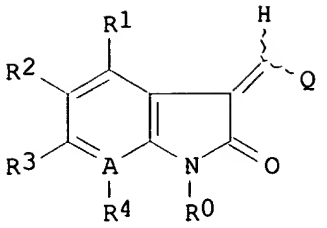
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9954684	A1	20000228	AU 1999-54684	19990804
JP 2002522452	T2	20020723	JP 2000-563824	19990804
US 6531502	B1	20030311	US 2001-762198	20010205
US 2002183364	A1	20021205	US 2001-13944	20011213

PRIORITY APPLN. INFO.:
US 1998-129256 A 19980804
US 1998-95470P P 19980805
US 1998-102178P P 19980928
US 1999-116107P P 19990115
US 1998-72023P P 19980121
WO 1999-US17845 W 19990804
US 1999-407164 A1 19990928

OTHER SOURCE(S): MARPAT 132:166123
GI



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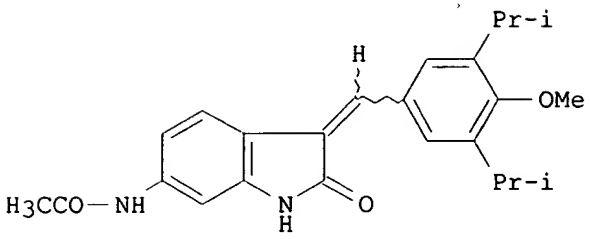


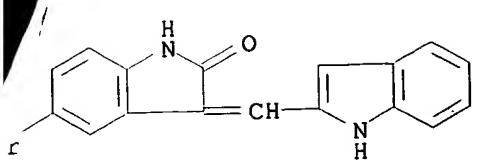
II

AB The title compds. (I) [wherein A = C or N; Q = substituted Ph, pyrrolyl, or indolyl; R0 = H, alkyl, C(O)R19, or C(O)OR19; R1 = H, (un)substituted alkyl, alkoxy, halo, aryl, (CH2)nOC(O)R19, or C(O)NR19; R2 = H, (cyclo)alkyl, (hetero)aryl, heteroalicyclic, trihalomethyl, alkoxy, halo, sulfamido, C(O)OR19, C(O)R19, NHC(O)OR19, (un)substituted amino, etc.; R3 = H, alkyl, trihalomethyl, alkoxy, aryl(oxy), heteroaryl, heteroalicyclic, OH, halo, sulfamido, C(O)R19, (un)substituted amino, etc.; R4 = H, alkyl, alkoxy, or halo; R19 = H, (cyclo)alkyl, alkenyl, alkynyl, or aryl; n = 1-4] were prepd. as modulators of the activity of receptor tyrosine kinases (RTKs), non-receptor protein tyrosine kinases (CTKs), and serine/threonine protein kinases (STKs). Examples include over 200 syntheses and data from seventeen bioassays. For instance, II was prepd. by a 3-step sequence involving: (1) cyclization and redn. of 2,4-dinitrophenylacetic acid with SnCl2.2H2O in EtOH to form 6-amino-2-oxindole, (2) amidation with AcCl in CH2Cl2, and (3) condensation of the amide with 3,5-diisopropyl-4-methoxybenzaldehyde. II was tested for HER-2 kinase activity (IC50 = 6.4 .mu.M), cellular proliferation activity as measured by the incorporation of bromodeoxyuridine (BrdU) driven by HER-2 (IC50 = 9.1 .mu.M) or EGF (IC50 = 11 .mu.M), and antitumor activity as measured by growth of SKOV3 ovarian carcinoma cells (IC50 = 2.6 .mu.M) or A431 human epidermoid carcinoma cells (IC50 = 2.2 .mu.M). The invention compds. are expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer, diabetes, hepatic cirrhosis, cardiovascular disease, and immunol. disease.

IT **258830-72-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of 3-methylidenyl-2-indolinones as protein kinase modulators for the prevention and treatment of cancer, diabetes, hepatic cirrhosis, cardiovascular disease, and immunol. disease)

RN 258830-72-7 HCAPLUS

CN 2H-Indol-2-one, 5-bromo-1,3-dihydro-3-(1H-indol-2-ylmethylene)- (9CI) (CA INDEX NAME)



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(d) FILE 'REGISTRY' ENTERED AT 20:06:42 ON 14 SEP 2003
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(b) L9        2 S (204005-54-9 OR 210303-58-5)

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(f) FILE 'REGISTRY' ENTERED AT 20:09:40 ON 14 SEP 2003
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(g) FILE 'REGISTRY' ENTERED AT 20:10:17 ON 14 SEP 2003
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(h) FILE 'REGISTRY' ENTERED AT 20:11:00 ON 14 SEP 2003
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L18           1 S L17

(i) FILE 'REGISTRY' ENTERED AT 20:11:49 ON 14 SEP 2003
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L20 2 S L19

(j) FILE 'REGISTRY' ENTERED AT 20:12:26 ON 14 SEP 2003
L21 1 S 258830-72-7

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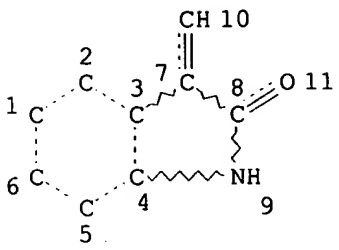

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

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